The development of Contextual Cognitive Behavioural Approach to Painful Diabetic Neuropathy

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Abstract

Painful diabetic neuropathy (PDN) affects 25-30% of people with diabetes. PDN is a debilitating condition and has significant impacts on the physical and mental wellbeing. Specifically, it is associated with poor quality of life, impaired sleep, physical disability and increased anxiety and depression. Pharmacological treatments for PDN have limited effectiveness and often intolerable side effects. Previous research suggested that psychological interventions may be beneficial for chronic pain, but only a few trials have been conducted specifically for people with PDN. Acceptance and Commitment Therapy (ACT) has growing evidence of its effectiveness for chronic pain. However, there is no study applying an ACT-based intervention to people with PDN. This thesis focuses on examining PDN within the framework of the psychological flexibility model and, relatedly, considering the potential usefulness of ACT for people with PDN. This thesis comprises of 3 studies.

Study 1: A systematic review examining and summarising evidence from observational studies of psychosocial factors and treatment trials of psychological interventions conducted with populations of people with PDN. Results suggest that sleep, quality of life, anxiety and depression are the most studied variables, within the PDN literature, and each is consistently associated with pain intensity. While only three Randomised Controlled Trials included psychological treatments applied to this population, there were promising results for their effectiveness. Evidence from commonly studied variables in chronic pain, such as coping or pain beliefs, was lacking in PDN research. Due to the lack of research, a study examining theoretically based psychosocial factors was suggested.

Study 2: The second study in this set was a cross-sectional survey investigating the association between facets of psychological flexibility (acceptance of pain, committed action, cognitive fusion and self as a context), and distress and daily functioning in people with PDN. Overall, 225 participants with PDN were recruited from hospital diabetes outpatient clinics and online. Through correlation analyses, acceptance of pain is shown to be negatively correlated with pain intensity,

pain distress, functional impairment, depression severity, and depression impact. Cognitive fusion correlated positively with pain intensity, functional impairment, depression severity, and depression impact. Committed action correlated negatively with functional impairment, depression severity and depression impact. In regression analyses, the combination of the four variables representing psychological flexibility accounted for significant variance in all equations except in the case of pain distress. The results of this study suggest that psychological flexibility may play a meaningful role in the context of PDN, and psychological treatment focused on psychological flexibility was indicated.

Study 3: The third study tested the feasibility of ACT among individuals with PDN in the UK. This was a single-cohort study of an online ACT treatment package, which was originally developed for chronic pain populations. Primary feasibility outcomes were recruitment, retention and treatment completion rates. Secondary outcomes were within-groups effects on pain outcomes and psychological flexibility. Process and outcome variables were measured at pre-treatment and 3 months post-treatment. The treatment completion rate was 40% for the ACT online treatment with all participants completing the follow-up questionnaires. Treatment completers demonstrated significantly lower levels of pain intensity and distress, depression and functional impairment and higher levels of committed action over time compared with non-completers. However, online ACT for people with PDN, seems to have limited feasibility and changes to the protocol, treatment content, and delivery may be needed before further testing in a larger feasibility study.

Certainly, further developments in treatments for people with PDN are needed. In turn, this will require greater attention to PDN by clinical researchers conducting studies of psychosocial processes linked to clinical outcomes. The set of studies described here produced preliminary evidence for a particular set of psychosocial factors and application of a psychological intervention for people with PDN, based on the psychological flexibility model. It provided some support for the feasibility of ACT,

including suggestive evidence around clinical outcomes. Further study of a modified ACT-based intervention in the healthcare context of the UK is suggested.

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Statement of contribution

This study was funded by Diabetes UK (DUK). The principal investigator was Professor Lance M. McCracken and the co-principal investigator was Dr Kirsty Winkley. The principal investigators, who were also my supervisors for this PhD, designed the study. My involvement began from the pre-funding stage. I coordinated the study and developed the studies' protocol under the supervision and guidance of the principal investigators.

The main aim of this DUK study was to identify potential modifiable psychosocial factors for people suffering from painful diabetic neuropathy, examine the potential efficacy and applicability of acceptance and commitment therapy (ACT), and implement a feasibility study to test the ACT based treatment. I generated all other hypotheses used in this PhD thesis. The use of the specific psychological and pain measures applied in this project was a decision which involved me and the principal investigators.

I carried out all three studies (systematic review, cross-sectional survey, feasibility study), collected and analysed the data and composed all papers which were submitted in peer-reviewed journals. Again, under the guidance and supervision of the principal investigators. I performed and adapted all the statistical analyses in this PhD thesis.

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Firstly, I would like to express my sincere gratitude to my supervisor and mentor, Professor Lance McCracken for this unique opportunity. He was my official primary supervisor up to the 2nd year of my PhD and continued to be actively involved in this project after his departure. His invaluable guidance, support, trust and insight have built up my confidence as a person and researcher. I would also like to thank Dr Kirsty Winkley, my second supervisor, who contributed greatly to my PhD, for her endless support, kindness and feedback and for generously offering her time over the past three years. Additionally, I am extremely grateful to Dr Emma Godfrey for stepping up as my official primary supervisor and for supporting and guiding me. Her help, time and inspiration have been very much important in shaping this research. Finally, I would like to acknowledge and thank my third supervisor Dr Whitney Scott for the faith she had in me, her time, invaluable feedback and help. Her input has helped me develop as a researcher. It was a real pleasure and honour to work with all these knowledgeable and respected academics.

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Glossary of Abbreviations

Abbreviation	Meaning
ACT	Acceptance and Commitment Therapy
AD	Amno Domini
ADA	American Diabetes Association
AIS	Acceptance of Illness Scale
ANOVA	Analysis of Variance
APA	American Psychological Association
BC	Before Christ
BDI	Beck Depression Inventory
BFNE	Brief Fear of Negative Evaluation Scale
BOS	Bristol Online Survey
BPI	Brief Pain Inventory
BPS	British Pain Society
CAQ-8	Committed Action Questionnaire-8
CBT	Cognitive Behavioural Therapy
CCM	Corneal Confocal Microscopy
CFQ-7	Cognitive Fusion Questionnaire-7
CI	Confidence Interval
CPAQ-8	Chronic Pain Acceptance Questionnaire-8
d	Cohen's d
DASS	Depression Anxiety Stress Scales
DBT	Dialectical Behavioural Therapy
DM	Diabetes Mellitus
DN4	Douleur Neuropathique en 4
DN4i	Douleur Neuropathique en 4 interview
DNS	Diabetic Neuropathy Symptom
DPN	Diabetic Peripheral Neuropathy
DSIS	Daily Sleep Interference Scale
DSM-IV	Diagnostic and Statistical Manual for mental disorders-fourth edition
DUK	Diabetes UK
EQ5D	EuroQol health outcome questionnaire
EQ-5D-5L	EuroQol five-dimensional questionnaire
FA	Fear-Avoidance
FAB	Fear-Avoidance Beliefs

FES-I	Falls Efficacy Scale-International
GDP	Gross Domestic Product
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-for Anxiety
HADS-D	Hospital Anxiety and Depression Scale-for Depression
HbA1c	Glycated haemoglobin
HCP	Health Care Professional
HFS	Hypoglycaemia Fear Survey
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic-pituitary-adrenal
HRT III RCM	Heidelberg Retina Tomograph III Rostock Corneal Module
HTAA	Hospital Tegku Ampaun Afzan
iACT	Internet-Delivered Acceptance and Commitment Therapy
IAPT	Improving Access to Psychological Treatment
IASP	International Association for the Study of Pain
IBM	International Business Machines
IDF	International Diabetes Federation
IENFD	Intra-Epidermal Nerve Fibre Density
IHPE	Institute of Health Promotion Board and Education
IQR	InterQuartile Range
IRR	Inter-Rater Reliability
ITT	Intention To Treat
IVR	Interactive Voice Response
JCBS	Journal of Contextual Cognitive Behavioral Science
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
MBCT	Mindfulness-Based Cognitive Therapy
mBPI-SF	Modified Brief Pain Inventory-Short Form
MBSR	Mindfulness-Based Stress Reduction
MeSH	Medical Subject Headings
MM	Mindfulness-based Meditation
MOPD	Medical Outpatient Department Clinic of Hospital
MOS	Medical Outcomes Study-sleep scale
MPQ	McGill Pain Questionnaire
MRC	Medical Research Council
NCS	Nerve Conduction Studies

NDS	Neuropathy Disability Score
NeuroQol	Neuropathy and Foot Ulcer-specific Quality of Life Instrument
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
N	Number
NNT	Number Needed To Treat
NPQ	Neuropathic Pain Questionnaire
N/R	Not Reported
NPS	Neuropathic Pain Scale
NPSI	Neuropathic Pain Symptoms Inventory
NSS	Neurological Symptom Score
OCD	Obsessive Compulsory Disorder
OR	Odds Ratio
PASS-20	Pain Anxiety Symptom Scale
PGIC	Participant's perception of treatment change
PhD	Doctor of Philosophy
PDI	Pain Disability Index
PDN	Painful Diabetic Neuropathy
PF	Psychological Flexibility
PHQ-9	Patient Health Questionnaire-9
PICO	Patient, Problem or Population/ Intervention/Comparison, Control, or Comparator/ Outcome(s)
PIS	Participant Information Sheet
PM	Progressive Relaxation Meditation
PPI	Patient and Public Involvement
PRISMA	Preferred Items for Systematic reviews and Meta-analysis
QOL	Quality Of Life
QOL-DN	Norfolk Quality of Life Questionnaire
QST	Quantitative Sensory Testing
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RFT	Relational Frame Theory
RR	Relative Risk
SCEDs	Single-Case Experimental Designs
SD	Standard Deviation
SE	Standard Error

SEQ	Self-Experiences Questionnaire
SF-12v2	Short Form Health Survey Version 2
SF-36	Short Form Health Survey
SMD	Standardized Mean Difference
SPSS	Statistical Package for Social Sciences
TAU	Treatment As Usual
TBAR	Thermal Biofeedback Assisted Relaxation
TB	Thermal Biofeedback
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TFA	Theoretical Framework of Acceptability
TSF	Tampa Scale of Fear of Fatigue
TSK	Tampa Scale of Kinesiophobia
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
WHO	World Health Organization
WHYMPI	West Haven Yale Multidimensional Pain Inventory
WSAS	Work and Social Adjustment Scale

Chapter 1: The problem of Diabetes Mellitus and Painful Diabetic Neuropathy

1.1 Chapter Overview

To give a context for the body of work presented in the present PhD thesis, this chapter will provide an overview of Diabetes Mellitus (DM). This overview will include a brief historical perspective, and then summaries of the prevalence, individual and socioeconomic impacts, and associated complications of DM. Treatment options will then be discussed, with a focus on monitoring blood glucose, dietary and physical activity management, oral anti-diabetic medication, insulin and injectable therapy. Finally, this chapter will provide a brief overview of research concerning Painful Diabetic Neuropathy (PDN). This overview will include a definition of PDN, brief description of the pathological process and diagnosis. Finally, the prevalence, impact, and management of PDN including pharmacological and psychological treatment options is reviewed.

1.2 Statement of the Problem

It is estimated by Public Health England (2016) that 3.8 million people in England have DM, either diagnosed or undiagnosed. There are many complications associated with this condition, but one of the most frequent complication is PDN. Approximately 20-25% of this population suffer from PDN (DUK, 2017). This has a large economic, social and personal impact on individuals (Institute for Health Metrics and Evaluation, 2017). Healthcare providers prescribe medication options to improve health outcomes and produce limited effects (National Institute of Neurological Disorders and Stroke, 2019). Psychological interventions may improve pain outcomes and help with condition management (Nathan et al., 2017), however, there are currently limited studies available to inform the development and evaluation of psychological interventions to people with PDN.

1.3 Introduction

The World Health Organization (WHO) defines DM as ''a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both'' (WHO, 1999). This disruption to insulin production or effectiveness causes blood glucose levels to rise (hyperglycaemia). High blood glucose levels are toxic to small blood vessels and, if sustained, this can lead to retinopathy (damage to the retina and therefore eyesight), nephropathy (kidney damage), and neuropathy (nerve damage) (Alberti, Zimmet, & Shaw, 2005; Holt & Hanley, 2012a).

Figure 1: Sculpture: Pain without words by Deborah Ann (Reproduced with permission)

The most common types of DM are type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is an autoimmune endocrine disorder and has traditionally been associated with diagnosis in childhood or adolescence, although more recent data suggests half of all cases are now diagnosed in adulthood (Thunander et al., 2008). T1DM is characterised by the destruction of β-cells within the pancreas which leads to a complete lack of insulin and then requires lifelong management with insulin injections or pumps.

T2DM is usually diagnosed after adolescence and results from depleted insulin production by β-cells and/or resistance to insulin (Alberti & Zimmet, 1998; Holt & Hanley, 2012b). The onset of T2DM seems to be associated with age, ethnicity, family history of diabetes and obesity (DUK, 2018). T2DM is also a major risk factor for complications, such as cardiovascular disease, as not only is hyperglycaemia problematic to the microvascular circulation in T2DM, it is also associated with high blood pressure (hypertension) and high levels of blood cholesterol (hypercholesteremia). These affect macro-circulation and therefore put the individual at increased risk of stroke and myocardial infarction (heart attack). DM is not only a problem of physical health but it is also associated with increased levels of anxiety (Grigsby, Anderson, Freedland, Clouse, & Lustman, 2002), depression (Anderson, Freedland, Clouse, & Lustman, 2001; Badescu et al., 2016) and psychological suffering (Polonsky et al., 2005). This results in significant, adverse, economic and social impact (Alberti et al., 2005). There seems to be a bi-directional relationship between mood disorders and diabetes and existing evidence shows that this may be due to shared pathophysiological mechanisms (Berge & Riise, 2015; Moulton, Pickup, & Ismail, 2015). Possible pathophysiological mechanisms are stress and cytokines. Both reviews (Berge & Riise, 2015; Moulton, Pickup, & Ismail, 2015), supporting these conclusions, explored the shared mechanisms between depression and diabetes. However, their definitions of depression differ and are not consistent with DSM-IV.

Another potential complication of DM is painful diabetic neuropathy (PDN), a persistent condition resulting from nerve damage or dysfunction, which leads to sensory loss and pain, in the feet and hands (Belapurkar, More, Patil, & Mohan, 2018) (See Figure 1). PDN arises in the peripheral nerve of either the autonomic or somatic nervous systems (Boulton et al., 2005). The primary cause of PDN is hyperglycaemia. Even though there has been progress to normalise glycaemia in diabetes with hypoglycaemic agents, dietary changes, and insulin, neuropathy continues to be a serious problem for people with DM (Holt & Hanley, 2012a).

1.4 Historical Background of Diabetes Mellitus

DM was first described in Egyptian papyri in 1500 BC, as a disease which caused patients to lose weight and urine quickly. Increased sugar, in blood and urine, was first noticed by the Indians (5th century BC) and was also mentioned in Greek medical texts (2nd century AD). DM was officially established by Dobson in Britain (1776). The term "diabetes" came from the Greek word *diabainein* (meaning "to come through") and was recognised by Araetus of Cappodocia (81-133 AD). The term "mellitus" came from the Greek word *meli* (meaning "honey") and was introduced by Thomas Willis (1675), because of the sweet taste of the blood and urine of patients with DM (Ahmed, 2002).

A milestone of great significance for experimental medicine was the discovery of insulin and the establishment of its therapeutic use for people with DM. Insulin discovery started with two concepts, introduced by Claude Bernard in France (1857): that DM is characterised by increased glucose production; and that the liver plays a significant role in glycogenesis. Mering and Minkowski (1889; Karamanou, Protogerou, Tsoucalas, Androutsos, & Poulakou-Rebelakou, 2016), proposed the role of the pancreas in the pathogenesis of DM, which in turn leads to the isolation of insulin islets and the therapeutic use of insulin for people with T1DM, by Banting and Best in Canada (1921) (cited in Holt & Hanley, 2012a). Insulin treatment meant that for the first-time people with DM could expect to live for longer. In 1955, the first orally administered anti-hyperglycaemic treatments, tolbutamide and carbutamide, were developed and tested in people with T2DM (Ahmed, 2002; Alhadramy, 2016).

1.5 The Epidemiology and Diagnosis of Diabetes Mellitus

DM is a major global public health problem which is steadily reaching epidemic levels (WHO, 2016). Between 1980 and 2014 the prevalence of people diagnosed with DM increased from 4.7% to 8.5% worldwide. In the UK 3,689,509 adults, or 6% of the population, have been diagnosed with DM (DUK,

2010, 2012; WHO, 2016). This dramatic increase is evident due to the continuous growth of population, unhealthy lifestyle, increasing lifespan, and obesity levels (Alberti & Zimmet, 2013; Hu, 2011; Narayan, 2006). However, the actual number of people who have the condition is likely much higher than this, as estimates suggest 630,000 people are undiagnosed (DUK, 2014). Worldwide, it is estimated by the WHO, that in 2014 approximately 422 million adults (≥18 years) were diagnosed with DM and this number is expected to double by 2025. The largest numbers were found in the Western Pacific, with 67 million people diagnosed with DM, followed by Europe with 53 million. Evidence suggests that India has approximately 40.9 million people with DM and China 39.8 million (Tabish, 2007) (See Figure 2).

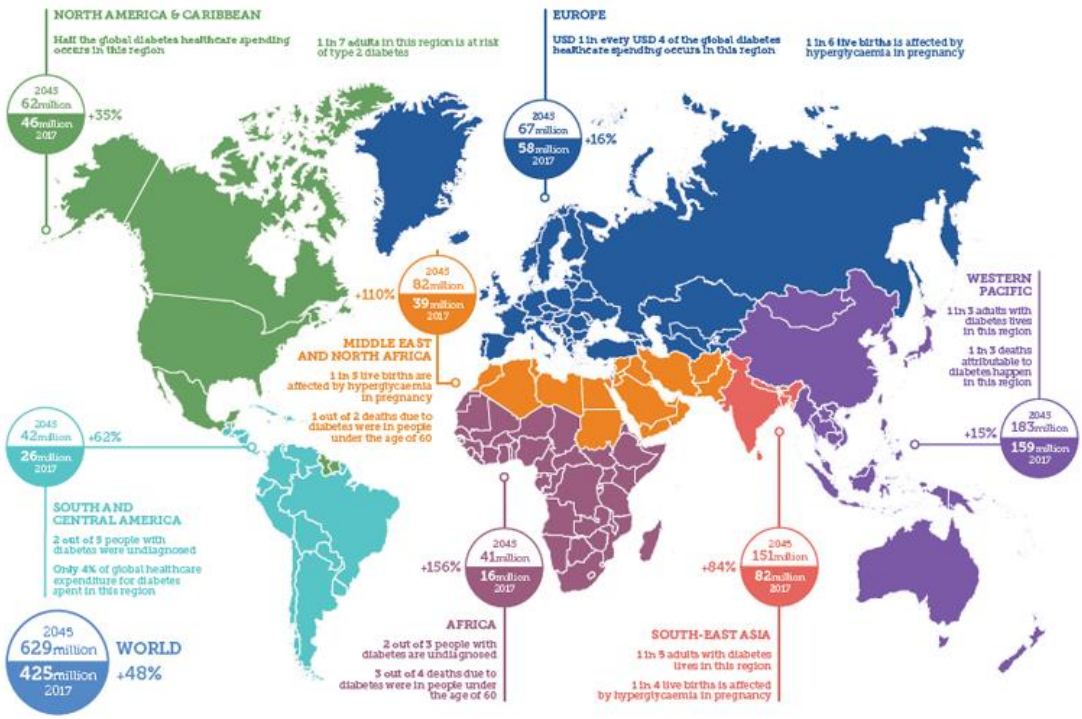

Figure 2: The latest figures, information and projections on diabetes worldwide (International Diabetes Federation, 2017; Reproduced with permission)

T1DM and T2DM are the most common types of DM, and it is estimated that 90% of people with a diabetes diagnosis suffer from T2DM and 10% from T1DM (NICE, 2015). However, there are no accurate global estimates for the exact percentage of people who are diagnosed with either T1DM or T2DM (WHO, 2016).

The diagnosis of diabetes is conventionally based on two abnormal glucose tests. Diagnosis of diabetes in a person with symptoms is made following an oral glucose tolerance test or an eight-hour fasting state test. An oral glucose tolerance test has questionable reliability because the produced results are influenced by the laboratories and adopted techniques, and is also expensive for the patients (Bennett, Guo, & Dharmage, 2007). The eight-hour fasting state test, has high specificity (mean 0.94, 95% CI: 0.92-0.96) and low sensitivity (mean 0.25, 95% CI: 0.19-0.32), which may lead to false or misleading results (Barry et al., 2017). In order to have an accurate and reliable diagnosis, both tests need to be used to evaluate the combination of the results (Holt & Hanley, 2012a). If the person is asymptomatic at least two blood glucose tests must be performed on different days, the results of which must both fall in the diabetic range which is 126 mg/dL (7 mmol/L) or higher.

Moving forward from the traditional methods of diagnosis, there is an additional test which includes measurement of glycated haemoglobin levels (HbA1c). Glucose in the blood plasma binds to haemoglobin molecules, waiting for the body to take in the erythrocytes (Bennett et al., 2007; Kilpatrick, Bloomgarden, & Zimmet, 2009). It is worth noting that the WHO provides a definition of HbA1c of ≥6.5% (≥48mmol/mol) for diabetes diagnosis, and HbA1c 5.7%- 6.4% (40-47 mmol/mol) for risk to develop diabetes (See Figure 3).

		Fasting plasma glucose		
		<6.1 mmol/L	≥6.1 – 6.9 mmol/l	≥7.0 mmol/L
2h plasma glucose following 75g oral glucose tolerance test	<7.8 mmol/L	Normal	Impaired fasting glycaemia	Diabetes
	≥7.8 – 11.0 mmol/L	Impaired glucose tolerance	Impaired fasting glycaemia *and* impaired glucose tolerance	Diabetes
	≥11.1 mmol/L	Diabetes	Diabetes	Diabetes
The American Diabetes Association defines impaired fasting glucose as 5.6-6.9 mmol/L Diabetes may also be diagnosed if random plasma glucose is ≥11.1 mmol/L				

Figure 3: WHO diagnostic criteria for diabetes, 1999 (Holt & Hanley, 2012a; Reproduced with permission)

In the UK, the National Institute for Health and Care Excellence (NICE, 2015) describes the diagnosis of T1DM when adults present hyperglycaemia and have one or more of the following: family history of diabetes, sudden weight loss, age below 50 years old, ketosis, BMI below 25 kg/m^2.

1.6 Treatment

T1DM is a result of an autoimmune metabolic disorder which destroys β-cells and may lead to the complete termination of insulin production. The suggested treatment for T1DM is insulin therapy, either through insulin injections or pumps. Additionally, the treatment plan for T1DM includes regular health checks and living a healthy lifestyle with a focus on increased physical activity and a healthy diet (Holt & Hanley, 2012a). These treatment options reduce mortality rates but increase the rates of individuals living long-term with T1DM and experiencing its complications (Alberti & Zimmet, 2013).

Therapeutic options for T2DM are major lifestyle modifications and behavioural changes, involving increased physical activity, diet and anti-diabetic medication, including injectable therapies such as incretin mimetics and insulin (NICE, 2019). As T2DM is a progressive disease, there is a notable loss

of β-cells over time and so supplementary insulin therapy becomes necessary (Smith-Spangler, Bhattacharya, & Goldhaber-Fiebert, 2012). In both T1DM and T2DM, blood glucose management is of crucial importance in order to avoid hyperglycaemia which is a strong predictor of cardiovascular diseases, stroke and other complications (Callaghan, Little, Feldman, & Hughes, 2012; Sherwani, Khan, Ekhzaimy, Masood, & Sakharkar, 2016).

National Health Service (NHS), Diabetes UK (DUK) and NICE provide guidelines for DM management. NHS and DUK advise individuals who suffer from DM not to skip meals, eat regularly, increase dietary fibre intake, consume five portions of vegetables and fruit per day, limit the consumption of alcohol and salt and keep hydrated (DUK, 2018; NHS, 2018). NICE (2015), highlights the importance of education in relation to the condition, physical activity, healthy eating, blood glucose and blood pressure management, and medication. Data from a systematic review (Orozco et al., 2008) demonstrated that increased physical activity and healthy eating reduced the risk of developing DM by 37% (95% CI: 0.49, *d*=0.79). While Boulé, Haddad, Kenny, Wells, and Sigal, (2001) found that increased physical activity reduced blood pressure, body weight, and waist circumference.

WHO (2005) defines adherence as "the degree to which the person's behaviour corresponds with the agreed recommendations from a health care provider". Another, more recent, proposed definition by Frost, Levati, McClurg, Brady, and Williams, (2017), describes adherence as “the extent to which individuals undertake a prescribed behaviour accurately and at the agreed frequency, intensity and duration (p.2)”. Many people diagnosed with DM face difficulties in managing their condition and adhering to recommended treatment (Gonzalez, Tanenbaum, & Commissariat, 2016). Evidence shows that in the US less than 1 in 5 adults, diagnosed with DM, are managing their condition as recommended by Health Care Professionals (HCPs) (Casagrande, Fradkin, Saydah, Rust, & Cowie, 2013). This refers to adherence behaviours in relation to medication, diet, physical activity, control of blood-glucose levels, monitor foot care and other complications (Gonzalez et al., 2010).

Non-adherence in T2DM is linked to complications, mortality, increased healthcare costs, emergency rooms visits, and inadequate glycaemic control. Poor adherence is also associated with demographic characteristics (i.e. low education level), nonpatient factors (i.e. lack of multidisciplinary care), and altered patient beliefs regarding their medications (i.e. treatment complexity) (Polonsky & Henry, 2016).

Adherence behaviours are influenced by various cognitive-behavioural factors according to the literature. A meta-analysis by Gonzalez et al. (2008), including 47 studies, demonstrated a strong link between depression and nonadherence to treatment. The reported weighted effect size was statistically significant of medium impact (r= 0.21, 95% CI: 0.17-0.25). However, the quality of the included studies was not assessed, making the evidence questionable. Other factors which have been linked to diabetes management and adherence are problem-solving skills, self-regulatory skills, emotional states, health beliefs (Gonzalez et al., 2016), and diabetes distress (Tareen & Tareen, 2017).

It is important to support individuals with DM though effective behavioural/psychosocial interventions to facilitate their self-management of diabetes and related distress (Peyrot & Rubin, 2007). According to the NHS, self-management is "a term used to include all the actions taken by people to recognise, treat and manage their own health. They may do this independently or in partnership with the healthcare system." The most commonly used interventions, aiming at behaviour change, are problem-solving and self-monitoring techniques, goal setting, coping skills, social support, incentives, environmental change, motivation enhancement, and behavioural contracting (Grey, Boland, Davidson, Li, & Tamborlane, 2000; Hardeman et al., 2005; Hill-Briggs, Cooper, Loman, Brancati, & Cooper, 2003; Rollnick et al., 2005). A meta-analysis by Harvey (2015) showed that, in people with T1DM, psychosocial interventions reduce HbA1c, noting a reduction of 0.48% in children and 0.22% in adults. In people with T2DM, a psychological intervention reduced

HbA1c by 0.76% (Harvey, 2015). These are significant findings, noting again that higher HbA1c increases the risk of developing diabetes-related complications (DUK, 2018). In this review, Cognitive Behavioural Therapy (CBT) was among the most effective interventions for reducing HbA1c (Harvey, 2015). A more recent Randomised Controlled Trial (RCT) conducted by Ismail et al. (2008), applied nurse-delivered motivational enhancement therapy with and without CBT in 344 adults with T1DM. Participants had DM for more than two years, HbA1c levels 8.2.%-15% and did not report any complications. This study found a significant reduction in HbA1c in the motivational enhancement therapy with CBT of 46% (95% CI: -0.81% to -0.11%) compared to the motivational enhancement group alone, of 19% (95% CI: -0.53% to 0.16%). Regardless of the importance of this evidence, this study did not achieve data completeness, as data was missing on the primary outcomes in 11.3% of participants. This intervention also, could not separate the effect of CBT as an addition to the motivational enhancement therapy, making the results more focused on the effectiveness of motivational enchantment therapy.

1.7 Impact of Diabetes Mellitus

DM has a significant socioeconomic impact on the global health system and the wider economy. Meanwhile the diagnosis and its related complications significantly affect the physical and psychological health of the individual.

1.7.1 Physical and Psychosocial Impact of Diabetes Mellitus

Evidence shows that DM has many significant negative impacts on the psychological and physical health of individuals; it impairs quality of life and increases anxiety and depressive symptoms. These are not only consequences of DM but, in turn, they also exert their own adverse health impacts and affect how individuals self-manage this long-term condition. A systematic review (Schram, Baan, & Pouwer, 2009) including 20 studies (two longitudinal and eighteen cross-sectional) and 11,494

participants, examined the association between depression and quality of life in people with diabetes. All studies found a negative association between depression and at least one aspect of quality of life. Even though the overall quality of the included studies was not assessed by the authors, the measures used within the studies were reliable and validated (i.e. SF-36).

A literature review from Clarke (2003), highlighted that there are numerous factors underlying the impact of DM on the individual. The most vital ones include age, since younger mean age is positively associated with increased emotional distress; and the individuals' perceptions of the severity of the condition, which may affect DM management. A large-scale follow-up survey (Sudore et al., 2012), including 13,171 participants (47% females, white, Hispanic, African-American and Asian, with mean age 60.0 $\pm$ SD 9.9), investigated the impacts on people with DM. Results suggested that 23.5% had depressive symptoms, and 24.2% had sleep impairment. Similarly, a cross-sectional survey (Collins, Corcoran, & Perry, 2009), including 1,456 participants investigated the presence of depression and anxiety in people with T1DM and T2DM which was assessed with the Hospital Anxiety and Depression Scale (HADS). Results suggested that 22.4% of respondents (95% CI: 20.2% - 24.7%) were suffering from mild/severe depression while 32% (95% CI: 29.5% - 34.6%) were suffering from mild/severe anxiety. This study had a high response rate (71%) from participants. The clinical significance of the results suggests the reliable conclusion that there is high prevalence of depression and anxiety in people with diabetes. A more recent cross-sectional study (Ugur et al., 2019), included 193 participants, 52 with T1DM, 86 with T2DM and 55 controls. This study assessed the prevalence of depression and anxiety using HADS, finding that participants with T2DM had reported significantly higher levels of depression and anxiety than participants with T1DM and controls. Interestingly, this study reported that, even though not significant, there was a positive correlation between HbA1C levels and depression (r=0.088, p=0.298) and anxiety (r=0.089, p=0.292) in participants with diabetes.

Pain seems to be another direct result of DM. Evidence shows that pain is associated with chronic fatigue in both T1DM and T2DM. One cross-sectional study, (Menting et al., 2016) including 214 participants, found that pain acts as a predictor for severe chronic fatigue and that is prevalent more in people with T1DM than T2DM. Results were statistically significant suggesting that 76% of participants had severe fatigue which persisted over time.

The literature indicates various potential mechanisms explaining links between diabetes and depression and anxiety. A literature review by Korczak, Pereira, Koulajian, Matejcek, and Giacca, (2011), suggested a biological link between T1DM and depression. Particularly, elevated circulating cytokines are linked to DM. This is a result from reduced insulin for metabolism, effects of iatrogenic hypoglycaemia, long-term hypoglycaemia, and/or hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Another literature review by Badescu et al. (2016), highlights that depression in T2DM is potentially linked with stress and inflammation. This result emphasises the importance of screening for depression in people with diabetes. This evidence, although useful, is of unclear quality. The review is presented more like a recommendation, to HCPs, to become aware that depression is a major co-morbidity, mostly undiagnosed, in people with diabetes.

The negative effects of DM are complex and bi-directional. Poor glycaemic management and poor uptake of therapies lead to high prevalence of depression in people with DM (Bogner, Morales, de Vries, & Cappola, 2012; Egede & Ellis, 2010; McSharry, Bishop, Moss-Morris, Holt, & Kendrick, 2015). Prevalence of anxiety and affective disorders are 85-123% higher in adults with DM than adults with no DM, and for diabetes distress and depression is 60% higher, which is explained by either the different use of psychotropic medication or by the fact that clinicians minimize patients' distress because they consider it to be normal (Fisher et al., 2008).

Besides the impact of DM on psychological wellbeing, society and the global economy, DM also has significant physical complications, which seem to be associated with the main socioeconomic costs

(Didjurgeit, Kruse, Schmitz, Stückenschneider, & Sawicki, 2002; Donahue & Orchard, 1992; Otterman et al., 2011). Research shows that retinopathy, kidney failure, blindness, and macrovascular complications, which lead to cardiovascular disease (Eckel, Grundy, & Zimmet, 2005), pain (Sudore et al., 2012), and diabetic neuropathy, which leads to limb damage, sensory and mobility loss (Tölle, Xu, & Sadosky, 2006) are the most common complications of DM. Given the focus on PDN in this thesis, further details on this specific complication, including prevalence and pathogenesis, will be provided in the final sections of this chapter.

While most diabetes education covers the potential for micro- and macro-vascular complications, few people are advised regarding the association with neurological deficits. There is growing research, however, that people with DM are at greater risk of vascular dementia (RR 2.0-2.5) and Alzheimer's disease (RR 1.5-2.0) (Biessels, Deary, & Ryan, 2008). A systematic review by Biessels, Staekenborg, Brunner, Brayne, and Scheltens, (2006), including 14 high quality studies, revealed that potential mechanisms linking diabetes with dementia and Alzheimer's include changes in glucose and insulin levels, and metabolism of amyloid-beta peptide. While there is not enough evidence to show which of these factors are the most clinically relevant, there is strong evidence suggesting that people with T2DM are at higher risk for developing dementia and cognitive impairment than people without diabetes. The main cognitive domains affected are mental speed, mental flexibility, learning and memory (Cukierman, Gerstein, & Williamson, 2005; Gregg & Caspersen, 2005; Xu et al., 2010).

In a recent meta-analysis by Cheng, Huang, Deng, and Wang, (2012) it was similarly found that the risk of developing dementia for people with DM is 1.46 higher than people without DM, and 2.48 times higher for vascular dementia. A Cochrane systematic review of 7 studies, including 4 RCTs, of people with T2DM, assessed the effect on cognitive function by type of intervention and level of metabolic control. This review found that no intervention was effective on the prevention or treatment of dementia and cognitive impairment. Based on moderate-quality evidence,

interventions were not different in their effectiveness on cognitive functioning in a period of 40-60 months (Sastre, Vernooij, González-Colaço Harmand, & Martínez, 2017).

1.7.2 Economic Impact of Diabetes Mellitus

DM has a substantial economic impact worldwide. Financial costs have increased by 26% from 2012 to 2017 due to the growing prevalence of DM (DUK, 2019). This includes direct and indirect medical costs and health resource expenditure. Direct medical costs result from medical management, such as hospital fees charged to patients and/or the health system. Indirect costs are a result of reduced productivity, increased absenteeism or lost wages. The health resource expenditures come from costs for prevention, medical care and rehabilitation (DUK, 2014; WHO, 2008, 2016).

In the UK, DM represents a huge economic burden as it is estimated that £23.7 billion per year is spent by the NHS for diabetes management and this number is expected to rise to £39.8 billion by 2035/36, meaning an increase of 13% of the worldwide public health burden (Barry et al., 2017). This amount includes £9.8 billion of direct medical costs, and £13.9 billion of indirect costs (Hex, Bartlett, Wright, Taylor, & Varley, 2012). Meanwhile diabetic neuropathy as a complication alone reaches approximately £100 million per year (DUK, 2014). DM is currently responsible for 10% of the total health resource expenditures in the UK (Hex et al., 2012).

In the USA the annual direct health care costs for diabetes alone due to outpatient visits and hospitalisation reach US$6,632 per person, while for diabetic neuropathy the current estimation is US$71,178 (Sadosky et al., 2015). The American Diabetes Association (ADA) estimated that in 2017 the total costs for people with diagnosed DM were US$ 327 billion. This amount includes direct medical costs of US$ 237 billion and indirect costs of US$ 90 billion, while health resource expenditures are estimated to US$ 9600 per person annually. One study predicted that in the period 2011-2030 losses in GDP worldwide would be in total US$ 1.7 trillion (Bloom et al., 2018). In particular, DM is estimated to cost US$ 800 billion for low- and middle-income countries and

US$ 900 billion for high-income countries, comprising both direct and indirect costs and health resource expenditure (Bloom et al., 2011). Another study including 699,042 people with diabetes showed that the largest costs for the healthcare system were a year after the diagnosis, more specifically the costs for women were US$3,785 per person (95% CI: 3708 - 3862) and for men US$3,826 (95% CI: 3751 - 3901) (Rosella et al., 2016). This data collectively highlights the enormous economic burden of DM.

1.8 Pathological Process and Diagnosis of Painful Diabetic Neuropathy

The pathogenesis of PDN is complex and involves a combination of processes which take place in the peripheral sensory nerves, at the dorsal horn of the spinal cord, and higher cortical centres (Schreiber, 2015). Prolonged hyperglycaemia in the peripheral nerves leads to the generation of reactive oxygen species and accumulation of advanced glycated end-products. This reduces the capacity of capillary membranes to vasodilate and influences the production and release of pro-inflammatory cytokines (Interleukines-1 and 6, Tumour Necrosis Factor-α) and nerve growth factors (insulin-like growth factor and platelet-derived growth factor). The results of these multiple mechanisms are disruption to the mitochondrial energy supply for epithelial cells, microvascular ischaemia, and damage to epithelial capillary linings (Shakher & Stevens, 2011; Tesfaye et al., 2010). See Figure 4 for more details.

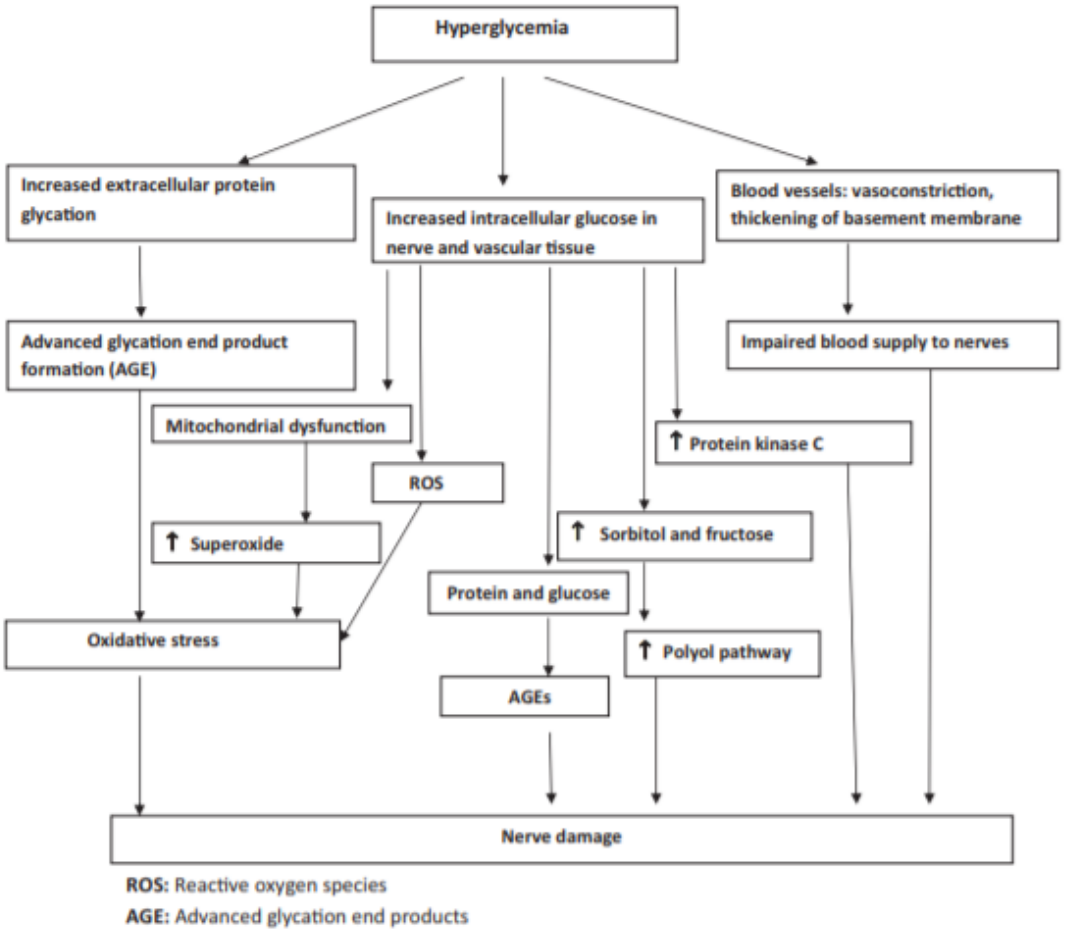

Figure 4: Pathogenesis of painful diabetic neuropathy (Kaur, Pandhi, & Dutta, 2011; Reproduced with permission)

These pathological processes start in the presence of severe hyperglycaemia and are specific to DM, appearing, on average, approximately after 25 years of the initial diagnosis (Kaur et al., 2011). Risk factors which seem to be associated with increased likelihood of developing neuropathy in people with DM are age (Kisozi et al., 2017), duration of diabetes (Barbosa et al., 2019; Mørkrid, Ali, & Hussain, 2010), hypertension (Barbosa et al., 2019), and hypoglycaemia (Papanas & Ziegler, 2015). Similar alterations in peripheral nerves seem to cause neuropathic symptoms following radiotherapy (Johansson, Svensson, & Denekamp, 2000), chemotherapy (Wolf, Barton, Kottschade, Grothey, &

Loprinzi, 2008), pharmacological treatments for human immunodeficiency virus (HIV) (Scott et al., 2018a) and high alcohol consumption (Chopra & Tiwari, 2012).

The multiple pathological and physiological processes can lead to the development of clinical symptoms, of PDN, which are burning, stabbing, aching and/or pricking senses, but the most common sensation is sharp pain, and clinical symptoms like bilateral numbness and/or pain in a sock and glove distribution (Gore, Brandenburg, Hoffman, Tai, & Stacey, 2006; Hoffman, Sadosky, Dukes, & Alvir, 2010; Kulkantrakorn & Lorsuwansiri, 2013).

A definitive clinical diagnosis of PDN includes the use of skin biopsy and intra-epidermal nerve fibre density (IENFD) to assess nerve fibres and functioning, assessment of sudomotor function, neurophysiology examination through nerve conduction studies (NCS) of sensory and motor nerves, or corneal confocal microscopy through Heidelberg Retina Tomograph III Rostock Corneal Module (HRT III RCM) (Petropoulos et al., 2018). The downside of these options is that they are highly invasive and not every patient is suitable for them. Table 1 includes a summary of common tests which are used to assess neuropathy.

Table 1: Common tests for neuropathy assessment (Akter, 2019)

Test	Advantage	Disadvantage	Type of Nerve
NCS	Sensitive, specific, reproducible, easily tenderized gold standard technique	Must be done by trained professionals	Large fibre
NDS	Good predictor for risk for ulceration	Does not detect sub-clinical large fibre damage	Large and small fibre
QST	Reproducible, reliable	Subjective	Large and small fibre
Skin biopsy	Gold standard, reliable, reproducible	Invasive procedure, needs specialized laboratory service	Small fibre
CCM	Rapid reproducible, non-invasive, can detect small fibre damage and track progression	Must be done by trained professionals	Small fibre

Note: CCM: corneal confocal microscopy, NDS: Neuropathy disability score, QST: quantitative sensory testing

Clinical signs and symptoms do not provide definitive PDN diagnosis but are used as screening tools. They are advantageous as they are easy to assess, non-invasive and have good sensitivity for identifying neuropathy, as indicated by the gold standard skin biopsy (Themistocleous et al., 2016). Some of the most frequently used interview-based self-report screening tools of autonomic, motor and sensory impairment are: Douleur Neuropathique en 4 (DN4) (Spallone et al., 2012), the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (Bennett, 2001), the Neuropathic Pain Questionnaire (NPQ) (Bouhassira et al., 2004), the Neuropathic Pain Symptoms Inventory (NPSI) (Dyck et al., 1980), the Neurological Symptom Score (NSS) (Meijer et al., 2002), the Diabetic Neuropathy Symptom (DNS) score (Krause & Backonja, 2003), and the McGill Pain Questionnaire (Melzack, 1987).

The Toronto Diabetic Neuropathy Expert group (Tesfaye et al., 2010) highlighted that diabetic neuropathies' diagnostic definitions include *confirmed neuropathy* where there is abnormal nerve conduction and a sign or symptom of neuropathy, *probable neuropathy* in which there should be

two or more signs of either decreased/absent ankle reflexes, decreased/absent distal sensation or neuropathic symptoms, and *possible neuropathy* where any of the signs below need to be evident: neuropathic sensory symptoms, decreased sensation, decrease ankle reflexes or symptoms of symmetric decrease of distal sensation.

The above-mentioned grading system has been upgraded by Finnerup et al. (2016). The new classification is the following: possible neuropathic pain, probable neuropathic pain and definite neuropathic pain. *Possible neuropathic pain* is characterised by the patient's history of a relevant neurological disease and the pain distribution which should be anatomically plausible with the possible location of the disease in the nervous system. *Probable neuropathic pain* requires a clinical examination which should confirm partial or complete sensory loss. *Definite neuropathic pain* involves the use of objective tests (e.g. skin biopsy). See Figure 5.

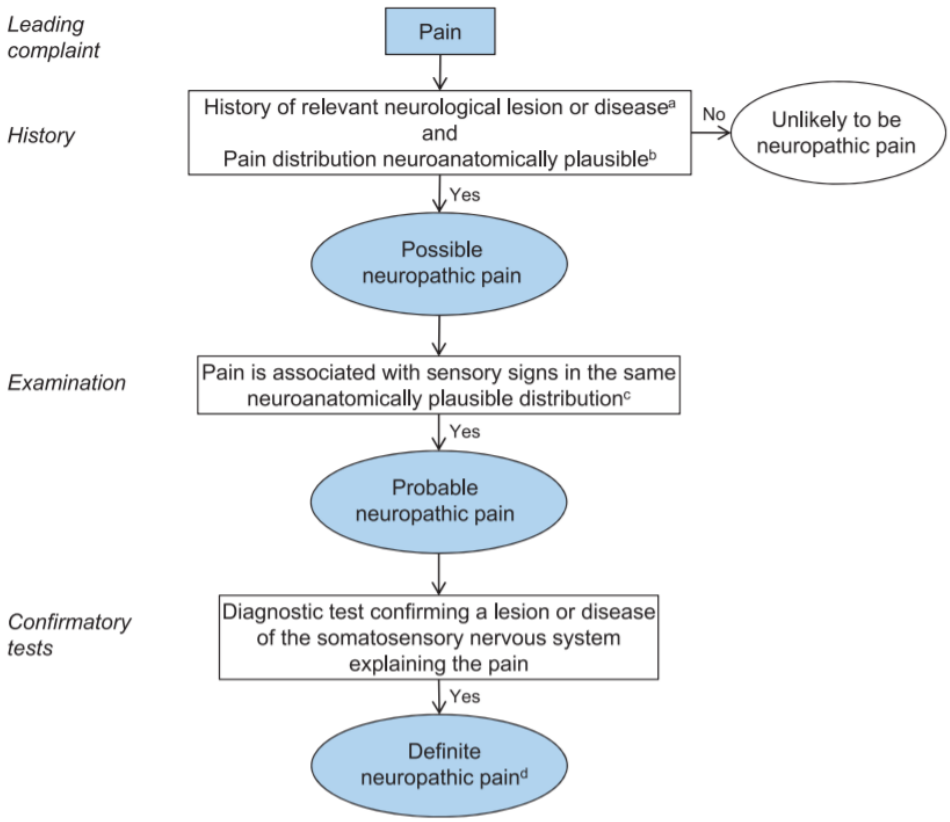

Figure 5: Upgraded grading system for neuropathic pain (Finnerup et al., 2016)

For the evaluation of PDN, it seems like simple clinical tests are most effective, while the most beneficiary strategy for early diagnosis is screening programs at frequent intervals. These programs may contain the nerve damage and also be cost-efficient (Gylfadottir et al., 2019).

Clinicians need to consider alternate diagnosis for diabetes-related neuropathy, such as neuropathy due to excessive alcohol consumption, musculoskeletal and vascular causes or vitamin B12 deficiency (Doupis et al., 2009; Hartemann et al., 2011). Nondiabetic neuropathies may be present in the DM population and may be manageable through specific treatment options, for example, physical therapy, anti-seizure and analgesic medications (Pop-Busui et al., 2016).

1.9 Prevalence of Painful Diabetic Neuropathy

Within the DM population, 16-23% are likely to develop neuropathy after 25 years of being diagnosed with DM (Daousi et al., 2004; Juster-Switlyk & Smith, 2016), which means approximately 600,000 people in the UK. Evidence shows that the prevalence is higher for individuals with T2DM (18%) than T1DM (6%) (Abbott, Malik, van Ross, Kulkarni, & Boulton, 2011; Hartemann et al., 2011). Table 2 includes further information on prevalence.

PDN differs in pain severity across patients. Cross-sectional studies (Gordois, Scuffham, Shearer, Oglesby, & Tobian, 2003; Tölle, Xu, & Sadosky, 2006; Zelman, Brandenburg, & Gore, 2005) demonstrate that 25-33% of people with PDN rate their pain as ‘severe’, 47-57% as ‘moderate’ and only 15-20% as ‘mild’, based on a common rating scale. The classification of pain categories is necessary for research, public policy and clinical evaluation (Zelman, Dukes, Brandenburg, Bostrom, & Gore, 2005). The last audit by the British Pain Society (BPS) in 2012, highlighted that neuropathic pain is common but under-studied. It is worth mentioning that not everyone with diabetes-related neuropathy experiences pain. Painful neuropathies are experienced by approximately 18% of people with diabetes and at least 30% of this population experiences painless neuropathies (Abbott et al.,

2011; Fedele et al., 1997; Miralles-García, de Pablos-Velasco, Cabrerizo, Pérez, & López-Gómez, 2010; Shaw, Zimmet, Gries, & Ziegler, 2003; Van Acker et al., 2009). Both types share the same risk marker, which is the relationship with obesity, but it is unclear which demographic and social factors are associated with each type (Spallone & Greco, 2013).

Table 2: DM & PDN Prevalence rates (DUK, 2017)

Country	DM diagnosis	Diabetic Neuropathy diagnosis
UK	3.7 million	16-23%
China	114.4 million	60%
India	>10 million	8-59%
USA	30.3 million	60%
Brazil	>10 million	50%
Globally	382 million	16-66%

1.10 Impact of Painful Diabetic Neuropathy

PDN mainly affects the hands, toes, legs, and feet and results in significant interference with mobility, balance, mood, social interactions, and overall quality of life. PDN has a great individual and socio-economic burden worldwide which seems to grow with higher pain severity (Alleman et al., 2015). A recent systematic review (Girach et al., 2019) investigating the quality of life in people with painful peripheral neuropathies from various aetiologies, included 66 articles of which 47 were concerned with participants with PDN. Results suggested that PDN leads to impaired quality of life and reduced physical activity. No further statistical analysis was conducted to reveal the effects of this association. This systematic review searched articles from only one database, Pubmed. The inclusion of more databases would possibly reveal more eligible articles.

It appears that PDN may impact on individuals' mental health through increasing levels of anxiety, catastrophic thinking, depression and fears (Geelen et al., 2017; Vileikyte et al., 2009) resulting, in

turn, in poorer outcomes overall, such as pain-related disability (Gore et al., 2005). Most patients report that their pain worsens at night, hence causing disturbed sleep (Zelman et al., 2006).

Severe pain of any kind is strongly associated with depression and anxiety (Campbell, Clauw, & Keefe, 2003; McCracken, Spertus, Janeck, Sinclair, & Wetzel, 1999). Existing evidence shows that PDN has a significant impact on anxiety, depression and catastrophic thinking (Jain, Jain, Raison, & Maletic, 2011; Selvarajah et al., 2014; Sullivan, Lynch, & Clark, 2005). This is consistent with results from a meta-analysis of 27 studies investigating depression in people with diabetes, demonstrating a significant correlation between depression and diabetes complications (r = 0.25; 95% CI: 0.22-0.28) (De Groot, Anderson, Freedland, Clouse, & Lustman, 2001).

Studies which examined the impact of PDN on sleep found that PDN is associated with disturbed sleep, low adequacy and quantity. Gore et al. (2005) conducted a community-based cross-sectional survey with 265 participants. Results found a strong association between PDN and sleep disturbance d = 1.46 (95% CI: 1.11 - 1.8). While two recent studies also found statistically significant effects between PDN and sleep disturbance, d = 1.12 (95% CI: 0.98 - 1.27) (Jacovides et al., 2014) and r = 0.30 ($p<0.001$) (Hughes et al., 2016). Taken together, these studies show that sleep is affected by PDN.

PDN also has an impact on occupational functioning. A cross-sectional study (N=1506) reported that 51.2% of individuals diagnosed with PDN had severe pain and were more likely to be unable to work than individuals with diabetes alone (4.74% PDN sample versus 3.49% diabetes alone sample) and to self-report as having an overall work impairment (19.77% PDN sample versus 13.75% diabetes alone sample) (DiBonaventura, Cappelleri, & Joshi, 2011). The main limitation of this study is that the sample was recruited online, so the results cannot be generalised, and the diagnosis is not confirmed by a clinician. The cross-sectional nature of the study does not allow us to infer cause and effect.

1.11 Management for Painful Diabetic Neuropathy

Treating PDN is challenging. People with rapid changes in glycaemic control are usually the ones who receive a neuropathy diagnosis (Gibbons & Freeman, 2009). As already described, existing evidence shows us that glycaemic control, targeted to reduce neuropathy development, and pain management, targeted to decrease symptoms severity, are the currently available treatment options. However, there is also promising research for effective prevention of the condition.

A review by Callaghan et al. (2012) found seven studies looking into treatments for T1DM. Two out of the seven studies were of high quality and a meta-analysis was possible, involving 1,228 participants. The review highlights that the only effective ways to treat nerve damage are glucose control and pain management. The results showed that patients who adhere properly to glucose control had an annualised risk difference of 1.84% for the development of clinically meaningful neuropathy. Eight studies for T2DM were used in a meta-analysis, including 6,669 participants. The results demonstrated no difference between participants adhering to glycaemic control approaches and those who have impaired glucose control. Overall, the review concluded that aggressive glycaemic control might be preventive for neuropathy in T1DM more than T2DM and that there is an urgent need for disease-modifying therapies, such as good glucose control, and not symptom-modifying therapies in order to improve patients' overall quality of life. According to a statement by the ADA, glycaemic control can slow down the progression of diabetic neuropathy in people with T1DM (78% approximate risk reduction) and with T2DM (5%-9% approximate risk reduction) (Pop-Busui et al., 2016). There was high-quality evidence in the included studies, which supported the benefit of enhanced glucose control in T1DM. Similarly, studies with moderate-quality evidence favoured enhanced glucose control in T2DM. However, it is worth noting that there was also high-quality evidence in adverse events, coming for enhanced glucose control, like weight gain and death (Callaghan et al., 2012).

A systematic review of 174 RCTs (Finnerup, Sindrup, & Jensen, 2010), and a meta-analysis of 229 RCTs (Finnerup et al., 2015) examined pharmacological treatments for neuropathic pain (not specific to PDN). The meta-analysis found that the number needed to treat (NNT; ≥50% relief) was 6.4 (95% CI: 5.2-8.4) for duloxetine, 7.7 (95% CI: 6.5-9.4) for pregabalin, 7.7 (95% CI: 6.5-9.4) for gabapentin, and 10.6 (95% CI: 7.4-19.0) for capsaicin patches. The evidence from these studies were of high quality for capsaicin patches and low for lidocaine patches. Overall the quality of the included studies was moderate. The evidence from these studies concludes that even when patients adhere to medication, they still experience pain and severe side effects. Given the existing evidence and impact of neuropathy on peoples' overall quality of life, there is an urgent need for early diagnosis and effective treatment (Yorek, Malik, Calcutt, Vinik, & Yagihashi, 2018).

In the UK when there is a neuropathic pain diagnosis there are several guidelines to be followed (NICE, 2013). NICE guidelines (2013) recommend Duloxetine as a first-line drug for PDN or Amitriptyline if the patient cannot take Duloxetine for any reasons (i.e. allergy). The guidelines recommend as a second-line drug, if the patient is on Duloxetine, to switch to Amitriptyline or combine with Pregabalin. If the patient was on Amitriptyline, it is suggested to combine this with Pregabalin. If these pain management treatments do not decrease pain, the third-line drug recommended is an opioid pain medication called Tramadol. NICE does not advise on the use of controlled opioid analgesics. The current guidelines (NICE, 2013) recommend HCPs and clinicians to select whichever course of action from Gabapentin, Pregabalin, Duloxetine and Amitriptyline according to patients' needs, reported side effects and personal history. If none of these options seems to be effective for pain, NICE suggests that the patient should be referred to speciality pain management clinics (see Table 3).

The most dominant form of treatment for PDN is the pharmacological one, which can lead to side effects including nausea, headache, dizziness and has limited effectiveness. Experiencing these side

effects often leads people to not adhere to medication (Quilici et al., 2009). Meanwhile, the burden of neuropathy due to diabetes is significant, including disability and suffering, while medical options are limited (McCracken, 2013). The management of PDN requires early diagnosis and a multifactorial approach (Javed, Hayat, Menon, Alam, & Malik, 2019).

Different types of pain usually do not require different types of psychological treatment, since any pain has a significant impact on peoples' lives with or without the specific neuropathy diagnosis (McCracken & Thompson, 2011). Evidence shows that most or all aspects of peoples' lives are affected both by neuropathic pain and by chronic pain in general (Closs, Staples, Reid, Bennett, & Briggs, 2009; Cohen, Quintner, Nielsen, & Guy, 2011; Duenas, Ojeda, Salazar, Mico, & Failde, 2016). Here chronic pain means "persistent or recurrent pain lasting longer than 3 months. p.2" (Treede et al., 2015).

For example, studies which compare people who suffer from neuropathic and non-neuropathic pain have found the two groups to be much more similar than expected. Daniel et al. (2008) conducted a controlled trial including 57 participants with low-back pain and 49 with postherpetic neuralgia, aiming to identify any physical or psychological differences between the two groups. The two groups did not appear to be different. Results were statistically significant and suggested that measures of pain acceptance, fear, mood and pain were similar for people with low back pain and postherpetic neuralgia. These results cannot be generalised to other populations. The findings are specific to people with postherpetic neuralgia attending pain clinics. Similarly, another study including people with trigeminal neuralgia and orofacial pain, found that the measures were no different on social and physical functioning, anxiety, depression and catastrophic thinking (Gustin et al., 2011). However, statistical significance was not found and the evidence may be altered if differences in medications between the two groups were taken into account.

Psychological treatments for PDN are limited and at a premature stage. This statement is supported by a recent systematic review we conducted (Kioskli, Scott, Winkley, Kylakos, & McCracken, 2019), identifying only three psychological treatments applied in the PDN population. After the undertaking of this systematic review, two more psychological treatments were identified. All five of them will be described and evaluated in detail below. In the case of other long-term conditions, like chronic pain in general, many psychological treatments have been applied to these patients, which may also prove effective and acceptable to the PDN population. Evidence and examples will be provided in Chapter 2.

Table 3: Medication options for Painful Diabetic Neuropathy according to NICE (2013)

Type of medication/Drug name	**NNT**	**NICE recommendation**
Tricyclic agents (TCAs)/ Amitriptyline	1.3	First line
Serotonin-norepinephrine reuptake inhibitors (SNRIs)/ Duloxetine	6.0	First line
γ-aminobutyric acid (GABA)/ Gabapentin	5.8	First line
γ-aminobutyric acid (GABA)/ Pregabalin	5.0	First line
Opioids/ Tramadol	3.8	Second line

Note: NNT: Number Needed to Treat

1.12 Summary

DM is a significant global public health challenge. It creates substantial individual suffering and economic burden. Existing research indicates a high prevalence of DM worldwide, which seems to be associated with psychosocial, health-care system, and economic factors. All these factors need to be taken into consideration to enhance the existing policies, promote the sustainability of healthcare and improve the therapeutic options for individuals who suffer from DM. It is clear that DM is a crucial health problem which needs to be treated as a priority.

PDN is a debilitating condition associated with DM, which, is also causing great suffering and disability for many people and producing its own significant associated costs worldwide. Existing evidence indicates high prevalence of PDN since approximately 30% of people with diabetes will develop this condition. Given the multifaceted nature of this problem, and paucity of research exploring psychological factors and treatment approaches, further research is necessary. People with PDN also deserve to be treated as a priority by both clinicians and healthcare systems. The next chapter will focus on existing behavioural models and psychological approaches to chronic pain.

1.12 Thesis Aims and Objectives

The overarching purpose of this thesis is to provide a better understanding of the psychosocial factors associated with people with PDN and assess the potential feasibility and acceptability of an Acceptance and Commitment Therapy-based psychological intervention in the same population.

Research question: Is the Psychological Flexibility model and Acceptance and Commitment Therapy treatment approach appropriate for people with PDN?

To answer this research question, this thesis proposed three specific aims:

1. To identify and evaluate the evidence of psychosocial factors and available psychological treatments associated with people with PDN.
2. To examine the relevance of the Psychological Flexibility model in a sample of people with PDN in the UK.
3. To explore the feasibility of an Acceptance and Commitment based treatment for people with PDN.

1.13 Thesis Layout and Chapter Format

This thesis incorporates publications arising during the PhD study period. The included studies are a systematic review, a cross-sectional survey and a feasibility study. With regard to timeline each study was conducted separately and not simultaneously. The results from the systematic review fed into the survey, by identifying the lack of studied psychosocial factors, and the results from both the systematic review and the survey guided, the feasibility study by highlighting the lack of psychological interventions and PF factors for the PDN population. This set of studies is considered an acceptable way to inform an intervention in the chronic pain literature.

The studies in chapters 3, 4 and 5 have been published and each of these chapters has an expanded unpublished format and discussion to allow integration of the chapters into a larger narrative and to highlight the links between studies. The appendices for these chapters can be found at the end of the thesis (see Appendix Q). Chapter 6 summarises how each of the chapters has addressed the thesis aims, outlines the strengths and limitations of the programme of work, integrates the findings into the wider literature, and discusses the clinical and theoretical implications of this thesis.

Chapter 2: Psychological Models and Treatments for Chronic Pain

2.1 Chapter Overview

This chapter will present conceptual and theoretical models of pain. These will include the biomedical model of pain and its historical background, and then psychological models, including the operant, the cognitive-behavioural, and the fear-avoidance models. Within the cognitive behavioural model, a detailed description of contextual cognitive behavioural approaches with a focus on Acceptance Commitment Therapy (ACT) will be provided. A literature review of psychological interventions for people with chronic pain, in general, is presented. Finally, this chapter includes evidence for the psychological treatment of Painful Diabetic Neuropathy (PDN) and highlights gaps in the literature.

2.2 Biomedical Model of Pain, and its Historical Perspective

Pain is a common human experience and has been defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (p.2)" (Rolf-Detlef Treede, 2018). Another, proposed definition, given by Williams and Craig, (2016) is: "pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components (p.2420)".

One key distinction is that pain can be acute or chronic. Acute pain is caused by an injury or as a result of a health condition and typically involves the musculoskeletal or sympathetic nervous system. Chronic pain lasts for three months or longer, which is generally regarded as past the normal duration of healing if an injury has occurred (Harvey, 1995). It may be musculoskeletal, sympathetic, visceral, or neuropathic (Grichnik & Ferrante, 1991).

In order to present a historical perspective on pain, selected key events will be discussed in this section. Starting in the 3rd century, Aelius or Claudius Galenus (better known simply as Galen, 129-210 AD), a Greek philosopher, surgeon and physician, located in the Roman Empire, focused his work on the human soul and spirit. His research in medicine, anatomy, and philosophy was innovative for the time and had a substantial impact on the study of pain perception and pathology. Galen was researching the pain experience and human body and identified, via dissection, that the circulatory system consists of two different systems. He reported that in the first system the liver produced venous blood which was then distributed throughout the whole body. Within the second system, he suggested that arterial blood was produced by the heart and once again was spread throughout the body. He also described multiple blood vessels which he referred to as 'mirabile' in the carotid sinus (Aird, 2011). His achievements within the field of medicine and anatomy led Galen to become interested in combining medicine and anatomy with philosophy and treat it as a multidisciplinary subject, which was innovative for the time. Based on his understanding of the circulatory system he developed a personality theory and proposed that mental health was influenced by physiology. After his death, his theories on circulation and personality, described above, were proven to be flawed and were vastly criticised (Gill, 2007). This fact revealed the urgent need for the development of a theoretical evidence-based model for science to progress.

Perhaps the next significant shift in history was when physicians started to view the body as a machine which moves continuously and consists of different parts. The earliest version of modern physiology was introduced by the French philosopher, mathematician and scientist, René Descartes (1596-1650 AD). His perspectives on physiology predominated within the medical professions across North America and Western Europe.

Descartes viewed pain in mechanistic terms and had a dualistic view of the mind-body interaction. He proposed the theory that animal spirits move through nerve tubes arriving at the pineal gland,

producing sensations corresponding to the magnitude of the physical motion of the spirits. Accordingly, Descartes viewed pain intensity as directly influenced by the degree of external stimulation or injury. This was an early example and a model of pain whereby pain was considered to directly correspond to the magnitude of injury or tissue damage. He depicted pain with an image of a boy who puts his foot directly in the fire and illustrating a string and a bell within his body (image from L'Homme see Figure 6). This represented a movement or touch starting from where the peripheral nerves end and then proceed to the brain, where it resulted in stimulation of the soul of the individual (Bonica, 1991; Procacci & Maresca, 1994).

Figure 6: René Descartes, L`Homme, (1632)

Descartes made another innovative contribution to the field of pain research by introducing the term 'central pain' to explain phantom limb pain. He used a female who had her arm and forearm amputated as an example. Descartes pictured active nerves going through her arm and forearm, which are capable to result into identical sensations, as if the woman would still have these parts (Rey, 1993).

In the 19th century, the concept of pain sensation was further specified, due to the evolution of philosophy and empirical studies. Johannes Peter Müller (1801-1859), introduced the "Law of

Specific Sensory Energies" which highlighted that the quality of sensations depends on the stimulated pathways and sensory organs (Kull, 1999; Müller, 1837). In 1858 there was a change in thinking with the development of "Specificity Theory" by Moritz Schiff (1823-1896). This theory stated that pain and touch are separate concepts with different peripheral and nervous system pathways (Schiff, 1859). In opposition to this theory in 1874 Wilhelm H. Erb (1840-1921), developed "Pattern Theory", which proposed that nerve stimulation, causing pain, is initiated by non-specific receptors. This means that any sensory stimuli may cause pain with the appropriate intensity.

The formal application of psychology to pain was introduced in the 20th century with the term 'psychogenic pain', which has a negative connotation and is defined as "pain which is independent of peripheral stimulation or of damage to the nervous system and due to emotional factors, or else pain in which any peripheral change (e.g. muscle tension) is a consequence of emotional factors p.170" (Merskey & Spear, 1967). Essentially, emotional experiences were linked to pain experiences (Binswanger, 1904; Titchener, 1908). Later, the definition and contrast of nociception and pain became evident where nociception was defined as "a physical reaction to a painful stimulus" and pain as "a subjective sensorial or emotional event" (Brooks & Tracey, 2005).

It is also worth noting that theories which focus on peripheral pathophysiology, are 'bottom-up' models to make sense of pain and are stimulus-driven influenced by physical factors. Subsequent theories included 'top-down processes', which are subject-driven and influenced by cognitive factors (Ossipov, Dussor, & Porreca, 2010).

In 1965 Melzack and Wall, made a breakthrough with the "Gate-Control-Theory" to describe mechanisms of pain. In this theory, mechanisms included emotional experiences and did not dichotomise pain as emotional or physical (Figure 7). This theory was proposed to update and extend all the existing theories of pain and was mainly influenced by Pattern Theory and Specificity Theory. Gate Control Theory did not exclusively focus on treating pain as the periphery. It

incorporated biopsychosocial aspects of pain and paved the way for psychosocial treatments in pain management (Melzack, 1969, 1991).

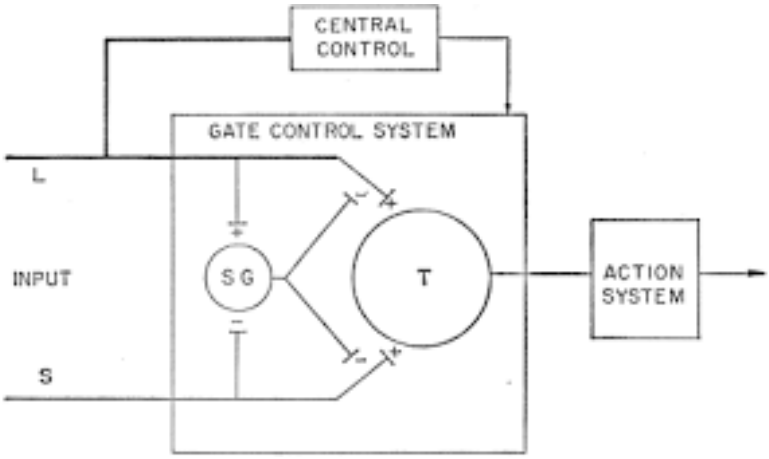

Figure 7: Gate Control Theory (Melzack & Wall, 1965)

Melzack and Wall proposed that noxious stimulation from the peripheral nervous system, allows nerve fibres to transfer information to the following destinations in the spinal cord: the dorsal column that projects towards the brain, the cells of the substantia gelatinosa and the central transmission cells in the dorsal horn. The interaction of these systems determines pain (Figure 8). The source stimulation comes from the following three places: central, other peripheral sites, and the “pain” location. Small nerve fibres represent 70-90% of all peripheral nerve fibres and are the first fibres to be damaged in diabetes (Smith & Singleton, 2008). While large nerve fibres are thicker (about 5 micrometres) because their axons are covered with a myelin sheath (Sveen et al., 2013).

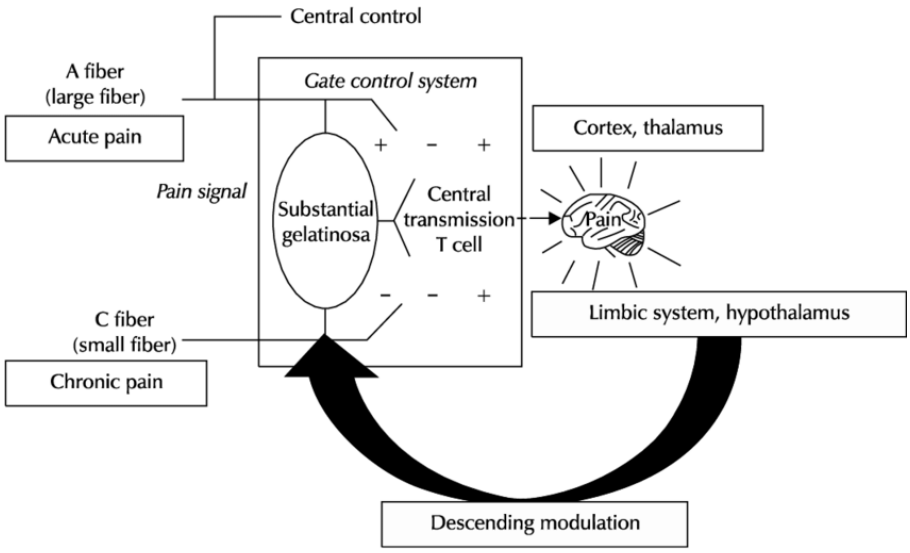

Figure 8: Physiology of Gate Control Theory (Cho & Min, 2015; Melzack & Wall, 1965)

Melzack (1990) extended the Gate Control Theory to the Neuromatrix theory of pain, which identifies brain regions involved in modulating pain. More specifically, the Neuromatrix theory (Figure 9) proposes that the perception of a painful stimulus results in the brain's active generation of subjective experiences, via a chain of neurons called the Neuromatrix (Melzack, 1990). The 'neurosignature' underpins the 'neuromatrix', which explains that psychological experiences, such as affective states and pain, and the genetic make-up, such as sensory and cognitive experiences, are unique to each person (Merskey, 1991). Even though both of the 'neurosignature' and 'neuromatrix' seem to be based on genetical factors, new experiences and learning can come to the equation and change the experience of pain.

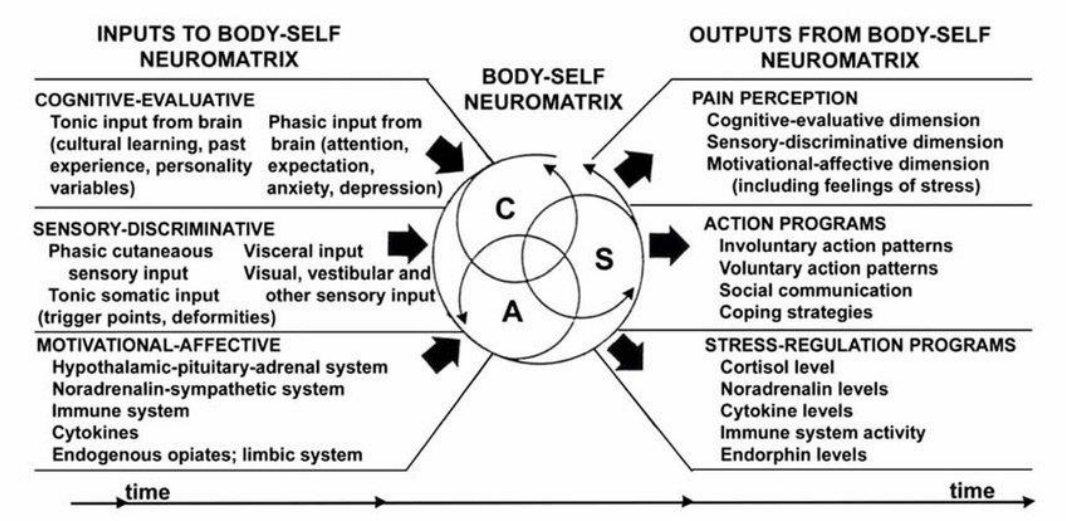

Figure 9: The body-self Neuromatrix theory (Melzack, 1999)

Following on from these theories, in the late 1960s, Fordyce presented a complete behavioural model of pain, the operant model, perhaps the first well developed modern-day psychological model. In 1983, Woolf introduced the central sensitization theory, an important theory highlighting that some pain conditions, even though persistent, have not been caused by tissue damage or ongoing injury (Moseley & Butler, 2015). Central sensitization is when the nervous system stays in a constant active state, and pain experience is present regardless of the original condition (Woolf, 2011).

Furthermore, it has an additive effect to continuously widespread pain and sensitivity to stimulation. It also results in poor sleep, emotional distress, anxiety and irritability (Mao & Kitz, 2017). According to the Institute for Chronic Pain (2015), central sensitization increases the reactivity of the nervous system, and leads to exacerbated pain.

Today, the main frameworks used by HCPs include the operant approach (Fordyce, 1976, 1982; Fordyce et al., 1973; Fordyce, Fowler, Lehmann, & Delateur, 1968), the cognitive behavioural approach, which is typically regarded as incorporating the operant (Turk, Meichenbaum, & Genest, 1983) and the central sensitisation theory (Woolf, 1983). Today most formal approaches

incorporate, or are based on elements, of the operant or cognitive behavioural approaches and this includes what are called “contextual cognitive behavioural” approaches.

2.3 The Operant Approach

The key defining feature of the operant approach was its focus on pain behaviour and pain-related disability (Fordyce et al., 1968; Fordyce, 1976). It emphasized the observable phenomena of pain, including avoidance, such actions as bracing and guarding, seeking help, moaning, complaining, coming from pain sufferers and reflecting for observers the presence of pain.

This framework incorporates operant conditioning principles of reinforcement described by BF Skinner, including social and non-social environmental factors in two ways. Firstly, through positive reinforcement; when the patient indicates the presence of pain, observers around them may react to the given signals and provide consolation or medication. These reactions may, in turn, reinforce the pain behaviour and increase its frequency. Secondly, Fordyce (1982) supported that through negative reinforcement or “avoidance learning”, which produces “behaviours, which serve either to escape a noxious stimulus, or to avoid or postpone a noxious stimulus (p. 319)”. This model incorporates the use of behavioural or learning principles and applies social factors to pain management. Therefore, Fordyce and colleagues (1968) used the operant principles to build innovative pain management programmes.

The operant approach appears to promote well-being, positive coping behaviour and to reduce pain behaviour. As applied to chronic pain, its primary proposed mechanism of action is the modification of environmental contingencies related to pain behaviour and “well” behaviour. Operant behavioural treatment involves the identification of the manipulatable events which are associated with patterns of pain behaviours and then the reduction of events that lead to higher rates of pain

behaviours and the increase in events that encourage effective, healthy, well behaviour (Roberts, 1981).

Furthermore, this approach is supported by evidence. Outcome studies from treatments that include operant principles have shown significant positive outcomes, although sample sizes have typically been small. An early treatment study of occupational and physical therapy, including 3 participants, reported a decrease of medication consumption and increase of physical activity after participants finished the pain management program (Fordyce et al., 1968). Another treatment study, implementing an operant conditioning program, with 36 participants, also reported a decrease in medication consumption and an increase in physical activity, for all participants both at post-treatment and follow-up (Fordyce et al., 1973).

Cairns and Pasino (1977), conducted an RCT implementing operant therapy to 9 participants suffering from chronic lower back pain. They reported that the experimental group increased their physical activity, compared to the control group. Roberts and Reinhardt (1980), conducted a trial including 26 participants in the experimental group, compared to a similar number rejected from participating in treatment, and reported that 77% of participants who completed an eight-week pain management programme eliminated their medication intake for one to eight years. Regardless of the importance of this study, most participants were lost in follow up making the results of limited clinical significance.

Turner, Clancy, McQuade, and Cardenas (1990), also conducted a trial with 96 participants, with chronic low back pain, who were randomised into the following groups: behavioural therapy in addition to aerobic exercise, solely aerobic exercise, solely behavioural therapy, and control group. This study concluded that the group receiving behavioural therapy in addition to aerobic exercise had significantly higher levels of functioning at post-treatment and follow-up. Follow up assessments

were not conducted making it ambiguous if the clinically significant effects were because of the received treatment.

There are potential limitations typically associated with the operant approach. First, the operant approach addresses the social context in treatment. However, the extent to which results from this context generalise and transfer to the patient's everyday social environment, including within their family relations, is unclear. For example, even if the treatment group alters contingencies during treatment, such as by praising helpful behaviours and ignoring disabling behaviours, the patient's spouse/family may continue to reinforce disability behaviours when they return home, such as offering too much assistance. Another major criticism of the operant approach is that it does not address the person's experience of pain, but only pain behaviours, and thus does not address thoughts and feelings about pain that contribute to distress and disability (Keefe & Gil, 1986). Furthermore, there is a remarkable lack of recent, high-quality RCTs to support the effectiveness of the approach (Williams, Eccleston, & Morley, 2012).

However, the operant approach did not aim to achieve pain reduction, or to necessarily focus on change in thoughts and feelings, but targeted disability reduction, nonetheless this criticism remains valid to a degree. Certainly, on the positive side, it is recognised that the operant approach highlighted the importance of applying psychological interventions for chronic pain treatment.

2.4 The Cognitive Behavioural Approach

2.4.1 Description of the Fear-Avoidance model

The fear-avoidance (FA) model currently plays a central role in the cognitive behavioural approaches (Figure 10). It appears to be one of the most important developments within this wider set of approaches (Philips, 1987; Vlaeyen & Linton, 2000). The FA model is a set of cognitive, emotional, and behavioural processes that naturally place fear and avoidance at the centre (Fordyce, 1976;

Lethem, Slade, Troup, & Bentley, 1983; Turk et al., 1983; Philips, 1987; Waddell, Newton, Henderson, Sommerville, & Main, 1993). It is worth noting that 'pain catastrophizing', "an exaggerated negative mental set brought to bear during actual or anticipated painful experience (p.524)," (Sullivan et al., 2001) is a crucial cognitive appraisal that contributes to pain-related fear and avoidance in this model. At the core of the model is the way people perceive pain, catastrophically or not, and how this may lead to two routes: one in which the interpretation of pain is non-threatening and so individuals continue to pursue physical activities and usual daily activities, which in extension can contribute to their recovery; or the other in which pain is interpreted as threatening, a catastrophe. The latter, can potentially lead to pain-related fear and avoidance of daily activities, resulting in a worsening of their condition (Vlaeyen & Linton, 2000).

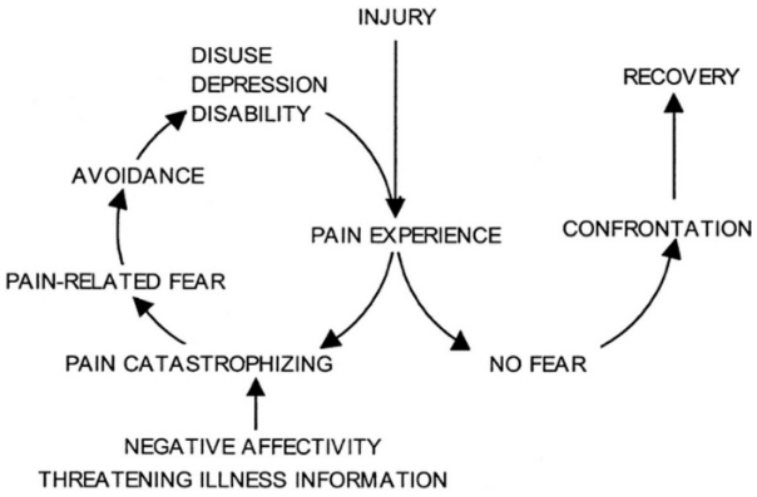

Figure 10: Fear-Avoidance Model (Vlaeyen & Linton, 2000)

Numerous studies have explored potential associations between the individual components in the FA model. Components examined include: catastrophic thinking; pain severity; attention to pain; vulnerability; disability; disuse; and avoidance. A literature review by Leeuw et al. (2007a), examined the existing scientific evidence for these components and their relationships. Results from the included studies suggested that catastrophising and excessive attention are associated with more pain and disability (Boersma & Linton, 2005a; Goubert, Crombez, & Van Damme, 2004; Leeuw et al.,

2007b; Peters, Vlaeyen, & Weber, 2005; Sullivan et al., 2005). Also, pain-related fear is correlated with pain, disability and avoidance (Boersma & Linton, 2005b; Goubert, Crombez, & Lysens, 2005; Turner, Mancl, & Aaron, 2004).

A more recent systematic review by Wertli et al. (2014), examined fear-avoidance beliefs (FAB) in patients with low-back pain and how these beliefs impact treatment efficacy. This review included 18 RCTs, and the examined treatments were: nonsteroidal anti-inflammatory drug versus placebo, graded activity versus usual care, physical therapy versus muscle conditioning on training devices versus low-impact aerobics, exercise versus usual care and multidisciplinary rehabilitation. Studies were of moderate quality according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool. Results indicated that for patients experiencing low-back pain for up to six months FABs were associated with worse outcomes for pain and disability, while decreased FABs were correlated with decreased pain and disability at follow-up. This systematic review concluded that FABs are associated with reduced treatment efficacy, but patients with high FABs are more likely to improve if these are addressed.

Even though the FA model has been a successful model for psychological treatment development and disability prevention, it also has several limitations (De Jong et al., 2005; Turk & Wilson, 2010). To begin with, this model is not broad enough, since evidence does not consistently support the proposed sequential process relationships within the FA model. In fact, many people experience chronic pain and disability in the absence of significant fear, and the model does not account for these cases (Wideman et al., 2013). The model does not recognise that patients are likely to have different levels of pain intensity and pain-related disability of different durations. Also, the FA model does not take into consideration other psychosocial factors which may contribute to pain and disability, such as anxiety not associated with pain, shame, guilt, or embarrassment (Pincus, Smeets, Simmonds, & Sullivan, 2010). It is evident that the model does not consider personal goals, social

context and/or positive processes of therapeutic change and can result in focusing on a narrow set of treatment methods (Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012; Turk & Wilson, 2010).

2.4.2 Description of the Cognitive Behavioural Approach

Turk and colleagues (1983), expanded Fordyce's behavioural theory of pain with the development of the cognitive behavioural approach to chronic pain. Cognitive behavioural approaches can be applied in many different ways, but the main idea behind them is essentially the same, that behaviour is regulated by a person's interpretation of the world. This approach was inspired by the development of cognitive behavioural therapy (CBT) in the 1960s, which is focused on examining the interplay between thoughts, emotions and behaviours (Beck, 1964).

In general, the goals of conventional forms of CBT are to increase adaptive beliefs and positive automatic thoughts. Further develop skills which will help with the management of negative feelings and emotions associated with pain, infuse a sense of hope and achieve behaviour change via conducting behavioural experiments, such as graded activity increase (Turk et al., 1983). Essentially, it aims to change the individual's focus and to establish reconceptualisation of the pain as non-threatening and manageable by one's own efforts. CBT uses specific learning techniques. Individuals are trained to become aware that their pain condition may worsen with stress, negative emotions, and decreased social support (Turk & Winter, 2006). They are encouraged to control their fear and avoidance, which are mostly associated with pain through various techniques such as graded exposure, and to control depression through behavioural activation and cognitive restructuring. CBT employs other techniques such as mindfulness, development of communication and problem-solving skills, and coping strategies (Keefe, Jacobs, & Edwards, 1997). These techniques aim to help individuals to take charge of their condition, manage the physical challenges and gradually return to their every-day routine (Thieme, Flor, & Turk, 2006; Turk, 2003). Another essential part of CBT is the

completion of homework assignments which encourage active learning and integration of changes into daily life (Turk, 2003). During treatment, future challenges are anticipated and planned for, and particular responses are adopted to prevent drop-out or relapse and encourage better long-term outcomes (Turk et al., 2008). As a result, individuals are encouraged to develop coping mechanisms and react appropriately to future setbacks.

There have been a number of systematic and literature reviews of studies of psychological interventions for people with chronic pain (i.e. Eccleston, Williams, & Morley, 2009; Morley, Eccleston, & Williams, 1999), and they all support the applicability and potential effectiveness of cognitive behavioural approaches to improve wellbeing and reduce pain. The most recent update of a systematic review (Williams et al., 2012), focused on the effectiveness of psychological interventions for people who suffer from chronic pain in general (excluding headaches). This review identified and included 35 RCTs overall in a meta-analysis. Results comparing psychological therapies with treatment as usual, revealed small to medium effects post-treatment, from -0.05 (95% CI: -0.19 to 0.09) to -0.19 (95% CI: -0.33 to -0.05), and almost none at follow up when the treatment group was compared to an active control group, from -0.15 (95% CI: -0.28 to -0.02) to 0.07 (95% CI: -0.18 to 0.05). While this study showed the potential effectiveness of cognitive behavioural approaches the effect sizes demonstrated were modest.

2.5 The Contextual Cognitive Behavioural Approaches

2.5.1 Functional Contextualism: Philosophical Underpinnings of Acceptance and Commitment Therapy

The first person to develop the term “contextual cognitive behavioural” as a description of a kind of CBT was Steven C. Hayes (Hayes, 1987). Hayes appears to have both established the term ‘clinical behaviour analysis’ and developed ‘relational frame theory’, as means to explain and guide the

analysis of language and cognition (Zettle, Hayes, Barnes-Holmes, & Biglan, 2016). Hayes used relational frame theory (RFT) to develop ACT as a form of psychotherapy (described in subsequent sections). RFT addresses how behaviour is influenced by verbal-symbolic processes. This theory proposes that the same processes that are involved in typical language development may also facilitate the emergence of human suffering. This is because verbal processes can relate any situation to any other situation, including pain and avoidance. Once this has happened the functions connected to those situations are then transferred across to related situations, so that pain, avoidance and suffering can appear anywhere (Hayes, Barnes-Holmes, & Roche, 2001).

The philosophical assumption guiding ACT is 'Functional Contextualism' (Biglan & Hayes, 1996). It importantly focuses not only on predicting and explaining behaviour, helpful and not, but also on changing behaviour (Hayes, 1993a). Functional Contextualism acts as a philosophical basis for some wings of present-day behaviour analysis, as "the development of an organized system of empirically-based verbal concepts and rules that allow behavioural phenomena to be predicted and influenced with precision, scope and depth (pp. 50-51)" (Biglan & Hayes, 1996). Functional Contextualism is underpinned by two assumptions, with important implications for research and practice. These include subject matter, "the act in context" and an epistemological assumption, "pragmatic truth criterion" (Hayes, Strosahl, & Wilson, 1999). Briefly, "the act in context" refers to the holistic contextual view of behaviour as the activity of the whole organism, interacting in and with a context that includes feelings, thoughts, and body sensations and that is considered functionally (Hayes, 1987). The "pragmatic truth criterion" as defined by Hayes et al. (1999) is "what is true is what works (p.133)" and refers to how knowledge generation is based on demonstration of the successful achievement of goals (Hayes, 1993b).

2.5.2 Psychological Flexibility Model

Psychological Flexibility (PF) is the contextual behavioural model of wellbeing and behavioural performance characterised by the ability to "contact the moment as a conscious human being more fully as it is, not as what the mind says it is, and based on what the situation affords, persisting or changing in behaviour in the service of chosen values (p.187)" (Hayes, Levin, Plumb-Vilardaga, Villatte, & Pistorello, 2013). PF is a psychological model including six main processes: acceptance, cognitive defusion, present-moment awareness, self-as-context, values-based and committed action (Figure 11). The processes have been characterised more recently as behaviour that is "open, aware, and engaged (p.160)" (Hayes, Villatte, Levin, & Hildebrandt, 2011).

Acceptance is the first process of ACT, which aims to enhance the willingness of individuals to become exposed to unpleasant experiences. *Cognitive defusion* targets the separation between an individual's thoughts and events without altering cognitive content, which means changing the interaction with our thoughts to create helpful functions. Another process promoted by ACT is b*eing present*, meaning to have on-going awareness of current events in a non-judgemental way. *Self-as-context* is the process of observing your own experiences without letting them affect you. *Values-based actions* reflect an individual's capacity to connect with qualities they hold as important, and to engage in actions that are personally meaningful. Lastly, *committed action* is the skill which empowers the individual to pursue the values-based actions, persist with them in the face of challenges, and to change goals when they are not workable. These processes are considered to interact and overlap in their influence on behaviour (Hayes et al., 1999; Hayes et al., 2011). Table 4 shows how each PF component applies to the PDN experience.

Table 4: Application of PF components in the PDN experience

Psychological Flexibility Components	PF Components Examples in PDN
Acceptance	'I will try to exercise even if my feet will hurt while doing it.'
Cognitive defusion	'My stinging pain is a bodily sensation which should not stop me from doing my chores.'
Contact with the present moment	'Amputation is not a possibility at the moment, thinking that it might be in the future is not helpful. I should focus on which is my reality now.'
Self-as-context	'I notice that my hands are in pain when a piece of cloth is touching them, however, I realise that I am more than this experience, or I am able to separate myself from this.'
Values-based actions	'I will do what matters to me despite my burning pain.'
Committed action	'When the numbing in my hands worsens, while I am in the middle of an action that matters to me, I will either change my approach or take small steps in the current one in order to complete the action.'

Each process of psychological flexibility has a corresponding process of psychological inflexibility. PF processes also show how inflexibility towards pain experiences may contribute to pain-related distress and disability (McCracken & Vowles, 2014). Not all components of PF have been studied to the same extent in the literature. For example, committed action and self-as-context are the least studied, even though existing data reveals its association with physical and psychological functioning and well-being (McCracken, 2013; McCracken et al., 2015).

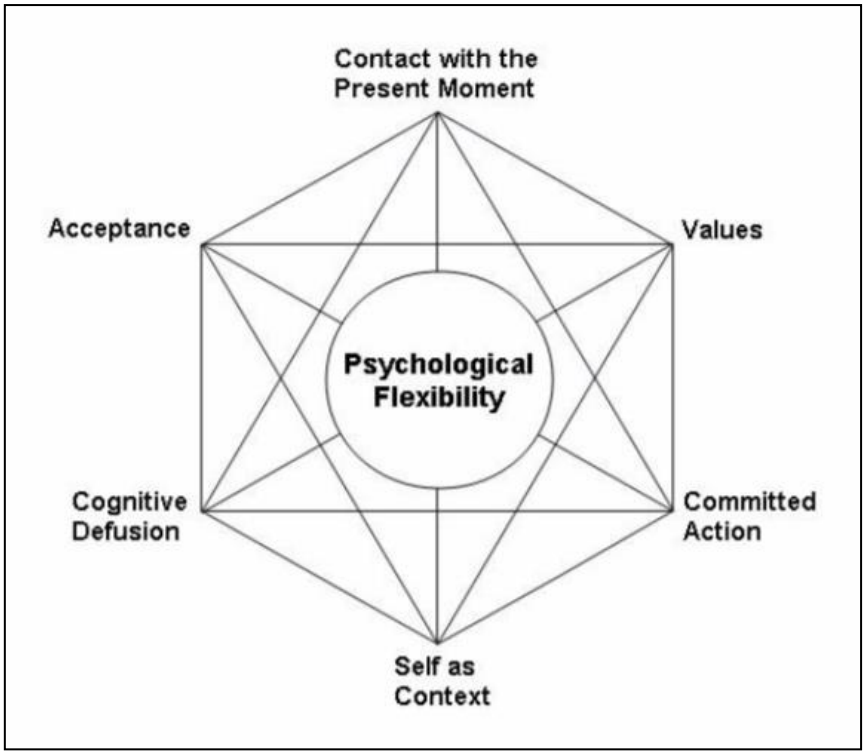

Figure 11: Acceptance and Commitment Therapy Model (Hayes, Luoma, Bond, Masuda, & Lillis, 2006)

2.5.3 Rule-Governed Behaviour and Relational Frame Theory

Rule-governed behaviour is an example of verbal behaviour. It refers to a specific behaviour arising from instruction-based learning or other verbal-learning patterns and procedures (Skinner, 1974). This specific behaviour is likely to become insensitive and persistent even when this is not helpful. History of verbal instructions given either by another individual, or by yourself, or by other learning methods (i.e. book, internet) is the base of a behaviour for following a specific set of rules (McCracken, 2005). An example of a rule which is followed is: If I have pain, that must mean I am damaging my body. Pain is therefore harmful. I must not move when I am in pain. This rule may work in the context of an acute injury. However, following this rule is impervious to the context of chronic pain, when pain no longer signifies harm.

Rule-governed behaviour (Hayes, 1987) and Relational Frame Theory (RFT; Hayes et al., 2001), are basic science theories associated with PF. PF processes are not technical definitions but are rather so called “mid-level” terms, which are easily applied by researchers and practicing psychologists (Williams & Craig, 2016). These two approaches are based on behavioural analysis and have acted as a philosophical base for ACT.

At the core of RFT is the term ‘verbal behaviour’ (Skinner, 1957). Verbal behaviour is contextually determined relational responding, where the “speaker” and “listener” behaviours are verbal. The most frequently used definition of verbal behaviour is “(a) a response is emitted by an individual; (b) the critical consequence is provided by the behaviour of another individual (the listener); (c) the listener's behaviour is explicitly conditioned to respond to the stimuli produced by the first individual; and (d) the explicit conditioning of the listener involves conditioning to arbitrary stimulus relations, probably conditioning to relational classes, for example, equivalence classes. (p.206)” (Chase & Danforth, 1991). Overall, relational framing is a core process by which rule-following and derived relational responding come to facilitate behavioural inflexibility and rigidity. In the case of PDN, pain responses and feelings could derive that pain response in novel contexts, by framing the new context as similar to or the same as a previous one associated with pain. Thus, for people with PDN, pain responses can transfer widely and lead to PF or rigid behaviours that do not help a person function or adapt well to the condition in many different life contexts.

2.5.4 ACT Treatment Techniques and Process

ACT is a form of psychotherapy based on the PF model (Hayes et al., 1999; Hayes et al., 2011). The ultimate goal of ACT is to enhance PF. According to the American Psychological Association, Society of Clinical Psychology (Division 12), ACT can be applied to people suffering from psychosis, depression, obsessive compulsory disorder (OCD), mixed anxiety and chronic pain, and has modest to strong research support (Gillen, Elefantis, Hodgson, & Henessy, 2013). Overall, patients with

chronic pain when allocated to a psychological intervention (i.e. ACT, CBT) are guided through the following broad technique categories: acceptance, mindfulness and commitment. They are generally advised to set goals based on their values, and then act upon these goals even if that means dealing with unpleasant experiences. See Table 5 for more information on distinctions between traditional CBT and ACT treatment techniques.

Table 5: Treatment techniques of CBT and ACT

Comparison of traditional CBT techniques with ACT techniques	
Cognitive Behavioural Therapy (CBT)	**Acceptance and Commitment Therapy (ACT)**
Pain education	Mindfulness strategies
Cognitive restructuring	Positive reinforcement
Graded exposure	Use of metaphors
Cognitive skills training	Use of paradox
Relaxation	Experiential exercises
Pacing/activity management	Identifying values
Problem solving/goal setting	Enhance PF
Communication skills training	Therapeutic alliance and stance
Physical exercise	Values-based goals setting
Key Shifts of Emphasis in CBT	
Cognitive Behavioural Therapy (CBT)	**Acceptance and Commitment Therapy (ACT)**
Focus on form/content	Focus on function
Symptoms	Performance
Method	Process

ACT does not have a single endorsed or approved protocol which may be used as a manual for psychological therapy (Yang & McCracken, 2014). However, there are several treatment manuals available that can guide clinicians (i.e. Hayes et al., 2011; Westrup & Wright, 2017). These treatment manuals give a detailed description of the role of the therapist, who is focused on the individualised use of metaphors and experiential exercises (Hayes et al., 1999) to achieve behaviour change and

enhance the PF of the individual (Luoma, Hayes, & Walser, 2007). The therapist plays a crucial role which is to encourage the individual to be goal-oriented, open, aware and engaged according to ACT's components. More specifically, the therapist should conceptualise momentary experiences (i.e. when someone is experiencing pain), remain sensitive to them and use these experiences to promote behaviour change to the individual. After the implementation of appropriate actions (i.e. set goals, use of metaphors) to promote PF, the therapist needs to assess the impact of these actions, and either persist with them or alter them according to the individual's needs. Some worksheet examples which are used during ACT therapy can be found in Appendix P.

ACT is differentiated from traditional didactic approaches, such as verbal persuasion or solely providing information. In a literature review by Yu and McCracken (2016), ACT-based interventions were described as focused on the increase of values-based and goal-oriented actions. This may be achieved through 'experiential methods' targeted at changing peoples' behaviour with exposure-based methods. These methods are usually metaphors, mindfulness exercises and role-play, among others.

2.5.5 Efficacy of the Contextual Cognitive Behavioural Approaches

Contextual approaches, which are more recent than behavioural therapy and CBT, are called 'third generation approaches' or 'third wave CBT' (Hayes, 2004). Some of these are based on Functional Contextualism, and others predate the development of Functional Contextualism. A feature that most of these contextual approaches have in common is that they do not intend to directly change feelings, thoughts or emotions but alter "the individual's relation to" these psychological events (Teasdale, 2003). There has been a rapid shift towards the development of contextual psychological treatments in the last 10 years (Harvey & Gumport, 2015).

Some examples of contextual cognitive behavioural approaches include mindfulness, which is based on the idea of being aware of the present moment and promotes observing in a non-judgemental

way (Kabat-Zinn, 1990); mindfulness-based cognitive therapy (MBCT), which is a psychotherapy approach combining mindfulness and CBT (Segal, Williams, & Teasdale, 2001); dialectical behaviour therapy (DBT) which supports the idea that some individuals react in a more intense way when they find themselves in an emotional situation (Linehan, 1993); and ACT (Hayes et al., 2006), which was discussed in the previous section.

There is a growing body of evidence supporting the efficacy of contextual-based interventions for people with chronic pain. A recent systematic review investigating the impact of internet delivered ACT (iACT) on people with anxiety conditions, suggested that 18 out of the 20 included studies found significant improvements after iACT delivery, with within-group effect sizes ranging from 0.32-2.14 (pre to post) (Kelson, Rollin, Ridout, & Campbell, 2019). Another systematic review examining whether ACT is helpful for people with cancer found that individuals who received ACT had great improvements in quality of life, increased PF and improved mental state (Gonzalez-Fernandez & Fernandez-Rodriguez, 2018). In a systematic review of 9 controlled and 13 uncontrolled studies by Veehof, Oskam, Schreurs, and Bohlmeijer, (2011), 19 contextual, "acceptance-based," interventions for people with chronic pain were identified and included, yielding statistically significant moderate effect sizes (SMD= 0.47-0.69) for depression, anxiety, wellbeing, quality of life and pain. Results from this study suggested that contextual interventions are as good as traditional CBT. This systematic review was updated recently (Veehof, Trompetter, Bohlmeijer, & Schreurs, 2016), this time including 25 RCTs of ACT and mindfulness approaches. Significant and small effect sizes were reported for disability (SMD=0.40, 95% CI: 0.01-0.79), pain intensity (SMD=0.24, 95% CI: 0.06- 0.42), and depression (SMD=0.43, 95% CI: 0.18-0.68). Moderate effect sizes were reported at post-treatment, for anxiety (SMD= 0.51, 95% CI: 0.10-0.92) and pain interference (SMD= 0.62, 95% CI: 0.21-1.03). Overall results indicated improvements in all outcomes at follow-up with small to large effect sizes (SMD= 0.41-0.66).

2.5.6 Challenges of Acceptance and Commitment Therapy and Future Considerations

ACT faces several challenges. These mainly include the question about whether it is truly an innovative or distinct treatment, if it is better than CBT in any way (Hoffman & Asmundson, 2008; Öst, 2008), and whether it is evidence-based and empirically supported (Öst, 2008, 2014).

Firstly, researchers and therapists who focus on ACT do not support the suggestion that it is superior to CBT. On the contrary, it is recognised that ACT has been influenced by other evidence-based therapies, like CBT, and this is the reason why it includes components such as behavioural activation, goal-setting, exposure, and skills training (Hayes et al., 1999). Even so, there are important differences from other forms of CBT, in terms of the underlying philosophical assumptions and treatment processes.

It is acknowledged that CBT is a recognised, established and evidence-based form of psychotherapy, while ACT is still relatively new with emerging, and therefore less, evidence to support its effectiveness (Yang & McCracken, 2014). However, the evidence is growing, for example in 2018, 50 RCTs were published which applied ACT to a range of conditions showing modest to strong evidence of its effectiveness. In addition, the American Psychological Association (APA, 2006) considers ACT as an evidence-based approach for chronic pain.

Future studies comparing ACT and CBT should consider examining the differences in key treatment processes, or perhaps seek some other method for progressing the field rather than head to head trials focused on clinical outcomes.

2.6 Online Treatment Delivery for Chronic Pain

In this modern era, the use of the internet has increased rapidly. Using the internet for delivering psychological interventions is growing in order to address issues of affordability and accessibility (Naylor, Naud, Keefe, & Helzer, 2010). The most commonly used so-called e-health interventions are

online CBT treatment programs (Eccleston et al., 2014; Ruehlman, Karoly, & Enders, 2012; Scott, Chilcot, Guildford, Daly-Eichenhardt, & McCracken, 2018), interactive voice response (IVR) (Liberman & Naylor, 2012), and videoconferencing (Yuen et al., 2019).

Online CBT-based treatment trials for chronic pain (Carpenter, Stoner, Mundt, & Stoelb, 2012; Dear et al., 2013; Schultz et al., 2018; Scott et al., 2018b) have been shown to be as effective as face to face therapy (Eccleston et al., 2014; Hedman, Ljótsson, & Lindefors, 2012), where main outcomes are designed to improve quality of life and functioning. Systematic reviews investigating the effectiveness and acceptability of online treatments yield small to moderate statistically significant effect sizes, while improvement in some factors, like anxiety, is inconsistent across the literature (Bender, Radhakrishnan, Diorio, Englesakis, & Jadad, 2011; Buhrman et al., 2013; Eccleston et al., 2014; Garg, Garg, Turin, & Chowdhury, 2016; Macea, Gajos, Daglia-Calil, & Fregni, 2010; Spijkerman, Pots, & Bohlmeijer, 2016). Online treatments differ vastly in content, duration, outcomes and retention rates (Eccleston et al., 2014; Jensen & Turk, 2014). The main issue with online treatments is potentially low retention rates. It is suggested that retention rates may improve based on the therapist, real-time responses and length of the treatment (Eccleston et al., 2014).

However, there are several limitations emerging from online treatment delivery which need to be considered. Firstly, some information given by the participant may be lost (i.e. due to disrupted internet connection), which may lead to problems such as diagnostic inaccuracy (Andersson & Titov, 2014). Also, it is unclear which group of patients may benefit the most from online treatment, for example, in terms of condition, age, gender, ethnicity (Andersson, Carlbring, & Grimlund, 2008). To continue, there are no specific measures to observe the negative outcomes for the patients who have not benefited (Nordgreen et al., 2012). High dropout rates and patients' non-completion of homework or online tasks are also considered major challenges for online treatments (Christensen,

Griffiths, & Farrer, 2009). Future studies are encouraged to further investigate the characteristics of people who are likely to mostly benefit from online treatment, since it is still unclear.

2.7 The Lack of Development in Psychological Approaches to Painful Diabetic Neuropathy

Certain pain conditions are well represented in the evidence of psychological treatments for chronic pain, such as chronic musculoskeletal pain, low back pain and fibromyalgia. Other conditions are not well represented. Research into psychological treatments for PDN is sparse and inconsistent. Many questions remain unanswered and this situation indicates the need for the development and application of effective, innovative and acceptable interventions. A recent systematic review (Van Laake-Geelen, Smeets, Quadflieg, Kleijnen, & Verbunt, 2019), examined the effects of physical therapy in combination to psychological interventions to improve quality of life for people with PDN, and found no existing studies reporting on multidisciplinary rehabilitation of that kind.

There are only five RCTs of psychological treatments for PDN (Hussain & Said, 2019; Nathan et al., 2017; Otis et al., 2013; Pfammatter, 2010; Teixeira, 2010) including treatments of mindfulness-based meditation (MM), progressive relaxation meditation (PM), mindfulness-based stress reduction (MBSR), CBT and thermal biofeedback (TB). This is inconsistent with the general chronic pain literature, where a highly selective systematic review identified 40 RCTs of psychological treatments for chronic pain in general (Eccleston, Hearn, & Williams, 2015); and the neuropathy literature, where a systematic review identified 14 studies (3 RCTs) with participants having any form of neuropathic pain and interventions of cognitive or behavioural context (Wetering, Lemmens, Nieboer, & Huijsman, 2010).

The MM study (Teixeira, 2010) included 20 participants in total (10 in the experimental group and 10 in the control group). Results showed a small between-group effect in the mindfulness group compared to the control on QOL, *d*= -0.16 (95% CI: -1.1 - 0.78), and a positive correlation of pain and

sleep in the overall sample *r*= 0.53 (95% CI: 0.048 - 0.813). This study had evidence of moderate quality due to the use of self-reported measures, small sample size and complete lack of follow-up measures. These limitations restrict the generalisability of the results to the diabetes population.

The TB study (Pfammatter, 2010), included 21 participants overall, 10 were allocated in the experimental group and 11 in the control group. The experimental group received 6 sessions with thermal biofeedback assisted relaxation (TBAR), while the control group received 6 sessions talking with a therapist about non-stressful events of life. Evidence from the biofeedback study was of very low quality and did not show any statistically significant effects between the experimental and the control group.

The CBT study (Otis et al., 2013), included 20 participants overall, 12 participants were allocated to the experimental group and received 11 weekly CBT sessions, and 8 participants received treatment as usual (TAU). Participants were assessed at baseline and at 4th month follow-up. Results suggested large between group effects in pain-interference, at post treatment *d*=0.91 (95% CI: 0.02 - 1.8) and follow up *d*=0.85 (95% CI: -0.03 - 1.74), large effects in pain severity, at post treatment *d*=0.88 (95% CI: -0.01 - 1.77) and follow up *d*=0.83 (95% CI: -0.05 - 1.71), and medium between group effects in depression, at post treatment *d*=0.68 (95% CI: -0.19 - 1.55). Besides the small sample size, the study was of high-quality which makes the evidence reliable. No harmful or adverse events were reported from the participants' involvement in the CBT programme as well.

The MBSR study (Nathan et al., 2017), included 62 participants (32 in the control group and 30 in the experimental group). Results suggested that within the experimental group, which received 9 online MBSR sessions, more than half of the participants (19/30) reported improvement in pain interference using the Brief Pain Inventory (BPI) (mean BPI score of ≥1.0), function, quality of life, depression and pain catastrophizing. Overall, the evidence was of high-quality. However, it is unclear which mechanisms of the intervention were successful and which not.

The PM and MM study (Hussain & Said, 2019) included 105 participants in total. Results showed that both groups reported reduction in their pain intensity, using the BPI, compared to baseline (28.7% and 39.7%, accordingly and $p < .05$). The MM group compared to the control meditation group, appear to experience more significant pain intensity reduction (of 5.2 ± 1.2 dropped to 3.0 ± 1.1 by week 12 of treatment and $p < .01$). The evidence was of high quality. However, the major limitations of this study were the use of self-reported measures and the lack of generalisability to other populations.

Nevertheless, the existing studies support the potential efficacy of psychological interventions for this condition. However, to date there have been no studies investigating the effectiveness of ACT on enhancing PF and improving the wellbeing of people with PDN.

2.8 Summary

This chapter has provided an overview of the biomedical model of pain and the shift in the understanding of pain over time. The operant approach was discussed as an important development of the biomedical model of pain towards an understanding of pain on behavioural grounds. This shift encouraged clinicians to treat pain more holistically, rather than just physically and initiated the development of psychological treatments for chronic pain. Even though cognitive processes such as coping, attention and beliefs did not appear in these stages, they now play a significant role in treatment development. Furthermore, this chapter has given an overview of the theoretical underpinning of ACT and psychological interventions that have been applied to the treatment of chronic pain in general, and PDN in particular. There has been a shift towards cognitive behavioural approaches for the treatment of chronic pain, which are focused on improving pain coping behaviours, beliefs around pain, attention to pain and emotional responses. The next chapter will present a systematic review of controlled and uncontrolled trials and survey studies, of psychosocial factors (i.e. depression, anxiety, sleep) for people with PDN.

Chapter 3: Psychosocial factors in Painful Diabetic Neuropathy: A Systematic Review of Treatment Outcomes and Survey Studies

3.1 Chapter Overview

As discussed in previous chapters, psychological models and treatment approaches appear to be beneficial to the wellbeing and functioning of people with chronic pain (e.g. Eccleston et al., 2015). Even though there is a large body of literature investigating the influence of psychosocial factors and effectiveness of psychological therapies in people with general chronic pain, the literature in PDN is relatively sparse. This chapter examines this literature. This includes a systematic review of evidence from treatment trials and survey studies in relation to psychological and social factors in people with PDN. The review also includes an assessment of quality for each study.

This chapter is published in the following article at Pain Medicine Journal (Appendix Q):

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Chapter naming and numbering are presented as they are in the published article.

3.2 Published Article

Manuscript Number: PME-RA-Aug-18-618.R1 - pnz071

Title: Psychosocial factors in painful diabetic neuropathy: a systematic review of treatment trials and survey studies

Article Type: Review Article

Corresponding Author: Lance M McCracken, PhD

Corresponding Author's Institution: King's College London

Authors: Kitty Kioskli, MSc; Whitney Scott, PhD; Kirsty Winkley, PhD; Stavros Kylakos, MSc

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Conflicts of interest: None declared.

Running Title: Psychosocial factors in PDN.

Note: This is the authors' accepted copy.

Abstract

Objective: Diabetes mellitus is associated with a number of complications that can adversely impact patients' quality of life. A common and often painful complication is painful diabetic neuropathy. The aims of this study were to systematically review and summarise evidence from studies of psychological treatments and psychosocial factors related to painful diabetic neuropathy and assess the methodological quality of these studies.

Methods: Electronic databases, related reviews, and associated reference lists were searched. Summaries of participants' data relating to the efficacy of psychological treatments, and/or to associations between psychosocial factors and outcomes, in painful diabetic neuropathy were extracted from the included studies. The methodological quality of included studies was assessed using two standardised quality assessment tools.

Results: From 2,921 potentially relevant titles identified, twenty-seven studies were included in this systematic review. The evidence suggests that depression, anxiety, sleep and quality of life are the most studied variables in relation to pain outcomes in PDN and are consistently associated with pain intensity. The magnitude of the associations ranged from small to large.

Conclusions: Research into psychosocial factors in painful diabetic neuropathy is unexpectedly limited. Available evidence is inconsistent and leaves a number of questions unanswered, particularly with respect to causal associations between variables. The evidence reviewed indicates that depression, anxiety, low quality of life, and poor sleep are associated with pain in painful diabetic neuropathy. The disproportionate lack of research into psychological treatments for painful diabetic neuropathy represents a significant opportunity for future research.

Keywords: painful diabetic neuropathy, psychological interventions, psychosocial factors, systematic review.

1. Introduction

Diabetes mellitus (DM) is highly prevalent and a significant public health problem (WHO, 2018). The International Diabetes Federation estimates that 425 million people are diagnosed with diabetes worldwide and these levels will rise to 628 million by 2045 (IDF, 2017) - it is a virtual epidemic. Common complications of DM include cerebrovascular and cardiac diseases, kidney failure, stroke, foot ulcer, blindness, and amputation (Brock et al., 2012; Dobrota et al., 2014). Another frequent complication of DM is painful diabetic neuropathy (PDN) affecting 25-30% of people with DM (Dobrota et al., 2014; Galer, Gianas, & Jensen, 2000; Spallone et al., 2011).

Existing literature on the epidemiology of PDN is heterogeneous, this is because of the differences in participants, settings, definitions of PDN, and assessment measures (Akter, 2019). For example, the Rochester Neuropathy study conducted by Dyck et al. (1993), included 380 participants with diabetes and assessed neuropathy via nerve conduction studies, neuropathy disability score and neuropathy symptom score. Results suggested that the majority of participants (66%), were diagnosed with some type of neuropathy from an unknown aetiology. The San Luis Valley Diabetes Study was a cohort study, including 279 people with diabetes which found that 25.8% of them were diagnosed with PDN (Franklin, Kahn, Baxter, Marshall, & Hamman, 1990). A more recent community-based study, which included 15.000 participants with a diagnosis of diabetes found that 34% of the individuals were showing symptoms of PDN, the main demographic characteristics of these participants were T2DM, South Asian origin, and women (Abbott et al., 2011). The European Diabetes (EURODIAB) Prospective Complications Study, which included 3000 participants from across 16 regions found 28% of PDN prevalence at baseline, with an increase of 23.5% after a period of 7 years. This study identified as risk factors: duration of diabetes, hypertension, cholesterol, triglycerides, smoking, obesity and age (Tesfaye et al., 2005). The Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study showed a reduction of 64% in the risk of

PDN in participants following intensive treatment, compared to conventional (Martin, Albers, & Pop-Busui, 2013).

PDN diagnosis is a clinical one and is based on the patient's description of pain, which is often described as a prickling, burning, deep aching, sharp sensation, similar to an electric shock (Kulkantrakorn & Lorsuwansiri, 2013). Subjective reporting of these painful symptoms can be used to screen for possible PDN; however, definitive diagnosis requires the presence of objective PDN signs (e.g., decreased ankle reflex) and findings confirming nerve dysfunction, such as using nerve conduction or through skin biopsy. While these objective indicators are required to confirm PDN diagnosis, for practical reasons, some studies rely on self-reported neuropathic pain symptoms for people with diabetes as an indicator of possible PDN (Galer et al., 2000).

More specifically, the ''gold standard'' for diagnosis is a skin biopsy, but this is invasive and not all patients are medically suitable for this. Another strategy is to screen for objective signs and symptoms. A third strategy is just to screen for symptoms through validated screening questionnaires which is the most efficient and least invasive. On the one hand, this reflects only 'possible neuropathic pain' (Finnerup et al., 2016). On the other hand, in health psychology research, screening only for symptoms is acceptable since we are interested in symptoms and their impact on quality of life rather than pathophysiology.

PDN primarily involves the toes, feet, and legs, and is associated with significant interference with mobility, sleep, mood, social interactions, and overall quality of life (QOL) (Barrett et al., 2007; Davies, Cramp, Gauntlett-Gilbert, Wynick, & McCabe, 2015; Geelen et al., 2017). PDN appears to significantly impact mental health, including anxiety and depression (Geelen et al., 2016; Vileikyte et al., 2005), which in turn contribute to poorer outcomes overall (Gore et al., 2005). Essentially, PDN is a chronic disease associated with long-term suffering and disability for many people (Mai et al., 2015; McQuay, 2002).

At present, most treatments for neuropathic pain are pharmacological (Edelsberg & Oster, 2009; Jensen, 2002; Marchettini et al., 2015). The ADA recommends optimization of glucose control to achieve the prevention or delay of PDN. The suggested first-line drugs, which targets pain management, are tricyclic antidepressants which aim to increase non-adrenaline and serotonin, and anticonvulsants like gabapentin, pregabalin and duloxetine (ADA, 2017). However, no single treatment has proven effective enough for pain relief or prevention (Javed, Petropoulos, Alam, & Malik, 2015). Findings are similar in the broader neuropathic pain literature. A systematic review of published and unpublished studies from 174 RCTs (Finnerup et al., 2010), and a meta-analysis of 229 RCTs (Finnerup et al., 2015) examined the medical management of neuropathic pain. The meta-analysis found that outcomes from trials were modest, including a number needed to treat (NNT; ≥50% relief) of 6.4 (95% CI: 5.2-8.4) for duloxetine, 7.7 (95%: 6.5-9.4) for pregabalin, 7.7 (95% CI: 6.5-9.4) for gabapentin, and 10.6 (95% CI: 7.4-19.0) for capsaicin patches. According to these results, even when PDN is treated with medication, many people continue to experience significant pain. These results suggest a need for new or additional treatments, potentially including non-pharmacological interventions.

Within the broader chronic pain literature, there is good evidence supporting psychological treatments, such as cognitive-behavioural therapy (CBT), for chronic pain (Bernardy, Klose, Welsch, & Häuser, 2018; Williams et al., 2012; Yu & McCracken, 2016). However, it appears that there are limited published studies of psychological treatments for people with diabetic neuropathies (Otis et al., 2013; Teixeira, 2010) and only one literature review examining physical and psychological interventions for people with PDN (Davies et al., 2015). This earlier review searched the literature up to July 2014 and identified only two psychological intervention studies. An updated review on this important topic appears due. It is also unknown which psychosocial factors might impact on outcomes in people with PDN, from a wider range of study designs. A wider view of psychosocial

factors could prove fruitful as it could lead to treatment developments that have not yet been conceived.

The purpose of this study was to synthesise and evaluate the evidence from trials of psychological treatments for PDN and other research into psychosocial factors in relation to PDN outcomes. From this we intended to (a) identify current psychological interventions for individuals who suffer from PDN and examine their effectiveness, (b) identify potentially modifiable psychosocial factors that might influence clinical outcomes associated to PDN and (c) assess the methodological quality of the included studies.

2. Methods

2.1 Registration

This systematic review protocol is registered with PROSPERO (registration number CRD42017060339) and may be accessed online at: https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017060339.

The current review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher, 2009) and established guidelines for narrative synthesis (Rodgers et al., 2009).

2.2 Search Strategy

We searched the following electronic databases, from 1946 to 10 August 2018: Medline, Embase, PsycINFO, Cinahl, Web of Science, ISRCTN registry, ClinicalTrials.gov registry, and EU Clinical Trials registry. Also, the reference lists of all included papers and related published reviews (Eccleston et al., 2015) were screened to identify any additional eligible studies. The PICO framework was used to develop the search strategy explicitly for the treatment trials. Our target population was patients

suffering from neuropathic pain due to diabetes. Included interventions were any study involving psychological treatments. In addition to treatment trials, observational studies examining relations between psychosocial factors and relevant outcome variables were also sought. All comparators were eligible. The selected outcomes were physical and emotional functioning, pain experience, pain-related interference with functioning, or QOL (see Table 6).

Furthermore, the Medical Subject Headings (MeSH) and free-text terms were divided into three groups: PDN, and psychological interventions or psychosocial factors, including all study designs, in order to identify both observational studies and RCTs (see TableS1 in Appendix E). Particularly, the Boolean Operator "OR" was used to enable identification of either relevant RCTs *or* observational designs measuring psychosocial factors in relation to pain outcomes in PDN.

Table 6: PICOS Inclusion/Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Population	Adults (minimum age 18 years) & Clear diagnosis of PDN	Children, adolescents (under 18 years) & Neuropathic pain due to other causes
Intervention	Any psychological treatment addressing psychosocial factors *or* studies measuring psychosocial factors for PDN and allowing the examination of these in relation to pain outcomes	Interventions that are only educational
Control	All comparators are eligible for this systematic review	-
Outcomes	Physical functioning Emotional functioning Pain experience Pain related interference Symptoms and adverse effects Quality of life	-
Study design	Any	Reviews
Publication type	Published full text articles	Unpublished dissertations and articles, editorials, letters/ Uncompleted trials
Language	English	Non-English articles

Note: "-": not applicable

2.3 Inclusion and Exclusion Criteria

We included any study involving psychological treatments incorporating any of the outcomes specified: physical or emotional functioning, pain experience, pain-related interference, or QOL, in individuals with PDN. Also, we included studies designed to investigate the association between psychosocial factors, for instance emotional responses, thoughts, beliefs, cognitive factors, or other behavioural patterns, and the designated pain outcomes. Studies examining potentially modifiable social processes, such as perceived quality of social support, in relation to pain outcomes were also included. Studies were excluded if they were not written in English or were not published as a full-text article. Additionally, studies that only investigated pain prevalence, and not the association between pain outcomes and psychosocial factors were not eligible. Studies that assessed only unmodifiable sociodemographic (e.g., ethnicity) in relation to pain outcomes were excluded. Studies were also excluded if they were solely educational interventions (meaning primarily focused on enhancing knowledge or providing information, rather than more active processes of psychological or behavioural change). This requirement is similar to the criteria set in the Cochrane review of psychological therapies for pain (Williams et al., 2012).

Participants within the included studies were adults, aged 18 years and older (at the time of their entry into the study), with a stated diagnosis of PDN. Studies of participants who suffered from neuropathic pain due to causes other than diabetes were not included.

2.4 Screening of Studies

After running searches in each electronic database, the predefined inclusion criteria were applied independently by two reviewers (KK; SK) in order to screen all potentially relevant titles and abstracts. After screening titles and abstracts for eligibility, the remaining potentially eligible full-text articles were reviewed for selection. Disagreements regarding eligibility were discussed, where

required, so that a consensus was reached. Disagreements that could not be resolved through discussion were settled from input by a third reviewer (LM, KW, or WS).

2.5 Data Extraction

The data extraction tool included the following: publication date; authors; country; journal; study design; types of interventions or psychosocial factors investigated; pain and related outcomes; participants' characteristics; study setting; study inclusion and exclusion criteria; recruitment method; reported medications; duration of PDN; outcome measures used; and statistical analyses (see Appendix D). The data were extracted from the eligible studies by three reviewers (KK, SK, or WS). KK extracted data from all studies while SK and WS each independently extracted data from approximately half of the studies. If the reviewers failed to reach a consensus on the extracted data, a third opinion was provided by another member of the research team (LM or KW).

2.6 Quality Assessment

The methodological quality of the included studies was evaluated using the Downs and Black (1998) quality assessment tool (Downs & Black, 1998) for observational studies or the Cochrane risk of bias tool for RCTs (Higgins et al., 2011), depending on the design of the study (see Appendices B and C).

The Downs and Black (1998) quality assessment tool has been identified as appropriate for the quality assessment in systematic reviews. It was applied to non-randomised trials and other observational studies. The checklist was modified minimally to meet the needs of the current systematic review. The methodological quality tool contained 27 items. The component ratings are divided as follow: A: Reporting, Score 0-10 (eight questions); B: External Validity, Score 0-3 (three questions); C: Internal Validity-Bias, Score 0-7 (seven questions); D: Internal Validity-Confounding, Score 0-7 (seven questions).

The Cochrane risk of bias tool (Higgins et al., 2011), is a widely used tool for assessing bias and flaws in the conduct, design, analysis and reporting of RCTs and is better suited to this than the Downs and Black tool. This risk of bias assessment tool includes: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

The checklists were administered by three independent reviewers (KK, SK, or WS) and cross-checked for consistency. Again, KK assessed all the studies and SK and WS each assessed half of the studies. Any disagreements were resolved by a third reviewer (LM or KW).

2.7 Data Analysis and Data Synthesis

Most studies investigated associations between more than one psychosocial variable and pain outcomes. The reported results are organised according to the specific psychosocial factors and pain outcomes included in the studies. The magnitude of relations from correlational methods was reported in terms of the correlation coefficient, *r,* when available.

Cohen's *d* was calculated by the first author (KK) to reflect effect sizes for between groups comparisons, based on means and standard deviations (SD) reported in each study. For variables that were assessed by more than one measure, a Cohen's *d* was calculated for each measure, and the final effect size reported for the variable was the mean of the Cohen's *d* of all measures (Muller & Cohen, 1989; Rosnow & Rosenthal, 1996). The calculated *d* values were interpreted, according to Cohen (1989), as small (*d*= 0.2), medium (*d*= 0.5) or large (*d*= 0.8).

95% Confidence Intervals (CIs) were calculated for Cohen's *d* and correlation coefficient *r* (for studies that reported a within-groups correlation coefficient). For Cohen's d, the 95% CI was calculated by first identifying the t-value and then using the 'ci.smd' function of the MBESS package in R (Lakens, 2018). The t-value was calculated as follows (Thalheimer & Cook, 2018):

$$t = Cohen's\ d\ \times \sqrt{\frac{Sample\ Size\ 1 \times\ Sample\ Size\ 2}{Sample\ Size\ 1 + Sample\ Size\ 2}}$$

For the correlation coefficient *r*, the 95% CI was calculated by first transforming the *r* to z', calculating the standard error for z', the 95% CI for z' and then transforming it back to values for r. The correlation coefficient *r* was transformed to z' with the following formula (Lane, 2018):

$$z' = 0.5 \times [ln(1 + r) - ln(1 - r)]$$

The standard error (SE) for z' was calculated by:

$$SE = \frac{1}{\sqrt{Sample\ Size - 3}}$$

The lower and upper bounds of the 95% CI for z' were found as follows:

$$Lower\ Bound = z' - 1.96\ \times SE$$

$$Upper\ Bound =\ z' + 1.96\ \times SE$$

Finally, the lower and upper bound values were transformed back to *r* values, by using the equation originally used to transform r to z'.

3. Results

3.1 Study Selection

The detailed selection process for included studies can be found in Figure 12. Each database was searched individually, and the total number of hits was 2,922. 2,226 articles remained after deduplication. After applying the predefined inclusion and exclusion criteria to the titles and abstracts, 41 articles remained for full-text review by the two reviewers. The manual search of the reference lists revealed seven more studies that did not appear during the electronic searches. At

the end of the screening and selection process, twenty-seven studies (twenty-nine published papers) met the criteria and were included in this systematic review.

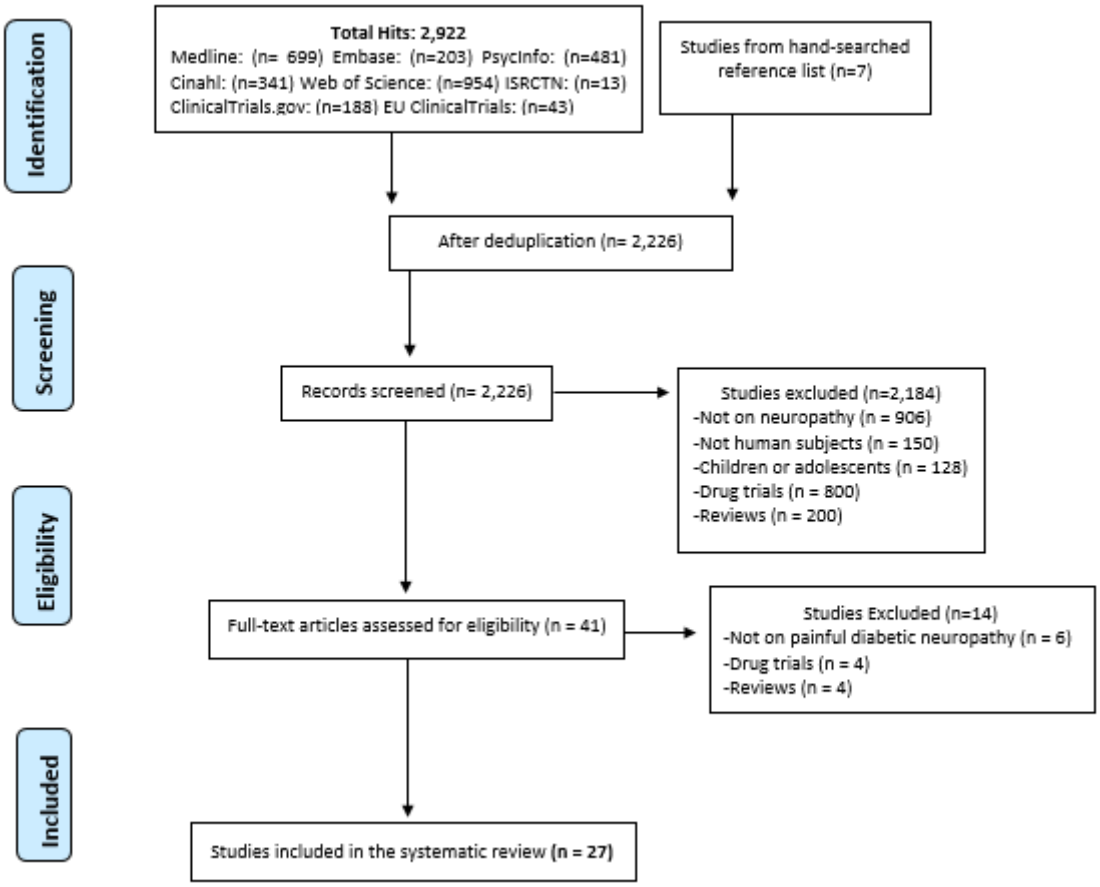

Figure 12: Flowchart-Selection process

3.2 General Study Characteristics

The twenty-seven studies found eligible for this systematic review were published between 1998 (Benbow, 1998) and 2018 (Levterova, Naydenov, Todorov, & Levterov, 2018). The majority of the studies (17/27) were cross-sectional (AL-Mahmood et al., 2018; Bouhassira, Letanoux, & Hartemann, 2013; Currie et al., 2006; Dobrota et al., 2014; Geelen et al., 2016; Geelen et al., 2017; Gore et al., 2005; Gore et al., 2006; Hoffman, Sadosky, & Alvir, 2009; Jacovides et al., 2014; Kulkantrakorn &

Lorsuwansiri, 2013; Levterova et al., 2018; Sadosky et al., 2013; Selvarajah et al., 2014; Themistocleous et al., 2016; Tölle et al., 2006; Van Acker et al., 2009; Vileikyte et al., 2005; Wickramasinghe, Subasinghe, Withana, & Wellala, 2016; Zelman et al., 2005; Zelman et al., 2006). Two studies were described as case-control (Benbow, 1998; Lewko et al., 2007), three as prospective cohort designs (Galer et al., 2000; Mai et al., 2015; Vileikyte et al., 2009) and three were RCTs (Otis et al., 2013; Pfammatter, 2010; Teixeira, 2010).

Most of the studies recruited participants from the USA (10 studies; 37%), the UK (6 studies; 22%) and the Netherlands (n=2; 8%). The remaining studies (9 studies; 33%), recruited participants from a range of countries across Europe, Asia, North and South America. The mean ages of participants and their standard deviations reported in the studies ranged from 45.9 ± 15 to 74.6 $\pm$ 10.8. 26 out of the 27 studies included both male and female participants, while one included only male participants (Otis et al., 2013). Detailed information regarding study characteristics can be found in Tables 5 and S2 (in Appendix E).

3.3 Clinical Characteristics of the Studies

Regarding the participants' clinical characteristics, 40.9% to 88.3% of the participants were taking medication for PDN. The most common medication types reported within the studies were: tricyclic antidepressants (33.5%), nonsteroidal anti-inflammatory drugs (26.8%), anticonvulsants (26.1%), and opioids (13.6%) (Benbow, 1998; Bouhassira et al., 2013; Currie et al., 2006; Geelen et al., 2016; Geelen et al., 2017; Gore et al., 2005; Hoffman et al., 2009; Jacovides et al., 2014; Selvarajah et al., 2014; Themistocleous et al., 2016; Tölle et al., 2006; Van Acker et al., 2009; Vileikyte et al., 2005; Wickramasinghe et al., 2016). Approximately 60% of the included studies did not report participants' use of pain medication.

Comorbid conditions were typically reported from 80% of participants in the included studies. The most commonly reported were congestive heart failure, hypertension, nephropathy, foot ulcer,

dyslipidaemia, retinopathy and fibromyalgia (Benbow, 1998; Bouhassira et al., 2013; Currie et al., 2006; Dobrota et al., 2014; Geelen et al., 2016; Geelen et al., 2017; Gore et al., 2005; Hoffman et al., 2009; Jacovides et al., 2014; Levterova et al., 2018; Selvarajah et al., 2014; Tölle et al., 2006; Van Acker et al., 2009; Vileikyte et al., 2005). 50% of the studies did not report participants' comorbidities.

PDN duration was not consistently reported. However, eleven studies included reports of participants time since PDN diagnosis (Bouhassira et al., 2013; Galer et al., 2000; Gore et al., 2005; Hoffman et al., 2009; Kulkantrakorn & Lorsuwansiri, 2013; Mai et al., 2015; Sadosky et al., 2013; Selvarajah et al., 2014; Teixeira, 2010; Tölle et al., 2006; Zelman et al., 2005). From the studies providing data, the PDN duration ranged from 2.4 to 7.8 years. 44% (12/27) of the studies did not report time since diagnosis (Table 7).

Table 7: Studies' general characteristics

Study	Design	Location	Recruitment Sites	Sample Size (n) per Group	Mean Age (years)	Male/ Female (%)	PDN Duration
AL-Mahmood et al. (2018)	Cross-Sectional	Malaysia	Medical Outpatient Department Clinic of Hospital (MOPD) clinic of hospital Tegku Ampaun Afzan (HTAA)	T: 90	65	60/40	-
Benbow (1998)	Case-control	UK	Adult hospital, diabetic clinic	T: 116, PDN: 41, DM: 38, C: 37	55.6	70/30	-
Bouhassira et al. (2013)	Cross-sectional	France	Hospital departments, private practice	T: 766, PDN: 156, T1DM: 297, T2DM: 469	48.3	55/45	At least 1 year at 57.4% of the participants
Currie et al. (2006)	Cross-sectional	UK	Hospital Trust	T:1125, T1DM: 236, T2DM: 889	64	56/44	-
Dobrota et al. (2014)	Cross-sectional	Croatia	Clinical hospital, university clinic for diabetes	T: 160, PDN: 80, DM: 80	62.4	52/48	-
Galer et al. (2000)	Prospective cohort	USA	Advertisements, newsletters, letters to physicians	T: 105	62.9	50/50	(diagnosed at 56.7 years of age) [SC]
Geelen et al. (2016; 2017)	Cross-sectional	Netherlands	Informative letter to regional hospital	T: 154	65.7	62/38	-
Gore et al. (2005; 2006)	Cross-sectional	USA	Primary care	T: 255	61.3	49/51	6.4 y

Hoffman et al. (2009)	Cross-sectional	Asia, Latin America, Middle East	Investigational centres	T: 401	57.3	38/62	2.73 y
Jacovides et al. (2014)	Cross-sectional	South Africa	Public and private outpatient clinics	T: 961, PDN: 291, DM: 670	55.9	51/49	-
Kulkantrakorn & Lorsuwansiri (2013)	Cross-sectional	Thailand	Internal medicine and neurology clinic at a University Hospital	T: 33	60.5	46/54	4 y
Levterova et al. (2018)	Cross-sectional	Bulgaria	University Hospital “Kaspela”, Plovdiv	T: 37	58.3	57/43	-
Lewko et al. (2007)	Case-control	Poland	Endocrinology, Diabetes and Internal Medicine clinics at the Medical University of Bialystok	T: 59, PDN: 22, DM: 37	61.3	18/32	-
Mai et al. (2015)	Prospective-observational	Canada	The Canadian Neuropathic Pain Database	T: 60	57.1	57/43	4.9 y
Otis et al. (2013)	Single-blind, RCT	USA	Advertisements in the Dept. of Veterans Affairs medical centre	T: 19, CBT: 11, C: 8	63	100/0	-
Pfammatter, (2010)	RCT	USA	Databases/Advertisements/ Posters	T: 21, BF: 10, C: 11	59.3	53/47	-
Sadosky et al. (2013)	Cross-sectional	USA	Community-based physician practices	T: 112	61.1	47/53	5.9 y

Selvarajah et al. (2014)	Cross-sectional	UK	Multidisciplinary outpatient service	T: 142	61.2	57/43	8.4 y
Teixeira, (2010)	Open label, RCT	USA	Medical practices and retirement communities	T: 20	74.6	25/75	7.76 y
Themistocleous et al. (2016)	Cross-sectional	UK	Primary care practices, diabetes clinics, teaching hospitals, neurology clinics, advertisements	T: 191, No PDN: 80 Mild PDN: 41 Moderate/Severe PDN: 70	67.23	45/55	-
Tölle et al. (2006)	Cross-sectional	France; Germany; Italy; Netherlands; Spain; UK	Community-based practices	T: 140	65.6	58/42	3-6 m: 14% 7-12 m: 22% 13-35 m: 43% ≥ 36 m: 61% [SC]
Van Acker et al. (2009)	Cross-sectional	Belgium	Outpatients diabetes clinics	T: 1111, PDN: 478, T1DM: 344, T2DM: 767	T1DM: 45.9 T2DM: 63.6	T1DM: 54/46 T2DM: 57/43	-
Vileikyte et al. (2005)	Cross-sectional	UK; USA	-	T: 484	61.86	70/30	-
Vileikyte et al. (2009)	Prospective cohort	UK; USA	-	T: 495	61.24	71/29	-
Wickramasinghe et al. (2016)	Cross-sectional	Sri Lanka	Diabetic Clinic	T: 235	56	35/65	-
Zelman et al. (2005)	Cross-sectional	USA	Primary Care	T: 255	61.3	45/51	6.4 y
Zelman et al. (2006)	Cross-sectional	USA	Primary Care	T: 255	61.3	45/51	6.4 y

Note: T: Total, DM: Diabetes Mellitus, T1DM: Type 1 Diabetes Mellitus, T2DM: Type 2 Diabetes Mellitus, C: Control Group, PDN: Painful Diabetic Neuropathy, CBT: Cognitive Behavioural Therapy, BF: Biofeedback, "-": not reported. Location: At the time, the location is provided to the lowest level reported (i.e. city). Recruitment sites: Where the recruitment site is not reported, recruitment methods are. Sample size: Sample sizes are provided in groups where given by the authors. Mean Age: Where the mean age is not reported, the alternative is. Only totals are reported. Male/Female: Only totals are reported. Where the % doesn't add up to 100, it means that there is missing data. PDN Duration: Most values are given as mean ± SD. y: years, SC: Galer provides the mean age when PDN was diagnosed for the sample; Tölle presents the duration of PDN in ranges of months and percentage of total sample falling within each range (Special Case)

3.4 Treatment Outcomes

Three out of the twenty-seven studies were RCTs of psychological treatments for patients suffering from diabetic neuropathies (Otis et al., 2013; Pfammatter, 2010; Teixeira, 2010). Please see Table 8 and Table 10 for more details.

Teixeira (2010), conducted a pilot trial of mindfulness meditation for PDN. The intervention group (n= 10) received training in mindfulness, and the control group (n= 10) received an "attention-placebo" treatment, for four weeks. The results indicated a small effect in the mindfulness group compared to the control on QOL. It was also found that pain and poor sleep were positively correlated in the full sample.

Pfammatter (2010), conducted a study of thermal biofeedback for PDN. The experimental group (n= 10) received six sessions of thermal biofeedback, and the control group (n= 11) six sessions with a therapist talking about non-stressful topics. Overall this study did not produce any statistically significant effects between the experimental and control groups, or any other consistent associations. Notably, 11 out of the 21 participants withdrew from the study.

Lastly, Otis et al. (2013) investigated CBT for PDN (n= 11), compared to treatment as usual (TAU) (n= 8). Results indicated that participants in the CBT group improved on pain severity and interference compared to the TAU group at four-month follow-up, but there was no improvement on depressive symptoms for either group. Results suggested large between group effects in pain severity and interference, both at post treatment and follow up. For depression, medium and small between-group effects were observed at and follow-up, respectively.

Table 8: Details of the psychological treatments' content

Study	Groups	Content	Duration	Frequency
Teixeira (2010)	Intervention/Attention-Placebo	Mindfulness Meditation/Nutritional Information and Food diary	20 sessions, 4 weeks, 60 minutes per session	5 days per week
Pfammatter (2010)	Experimental/Control	Thermal Biofeedback Assisted Relaxation/Discussed about benign topics with experimenter	6 sessions, 6 weeks, 15 minutes per session	Twice a day
Otis et al. (2013)	CBT/Treatment As Usual	Cognitive-behavioural pain management therapy/Continued receiving their usual treatment by their healthcare providers	11 sessions, weeks, 4 months, 60 minutes per session	1 day per week

3.5 Depression and Pain Outcomes

Eight cross-sectional studies (Bouhassira et al., 2013; Dobrota et al., 2014; Gore et al., 2005; Hoffman et al., 2009; Selvarajah et al., 2014; Themistocleous et al., 2016; Vileikyte et al., 2005; Wickramasinghe et al., 2016) investigated the role of depression in relation to pain in PDN (Table 10). Two studies investigated the association between depression and pain outcomes and reported large, positive effect sizes (Dobrota et al., 2014; Gore et al., 2006), one reported medium (Selvarajah et al., 2014) and another small (Vileikyte et al., 2005) (Table 10).

One study found that depression and pain severity are positively, but weakly associated. This was a cross-sectional study which did a group comparison in three regions (Asia, Latin America, Middle East) (Hoffman et al., 2009).

Three studies investigated depression in relation to pain, but data (mean and SDs) were not available to compute the effect sizes. One study (Bouhassira et al., 2013) reported that participants with chronic pain with neuropathic characteristics had higher depression scores than participants without neuropathic pain. One study (Themistocleous et al., 2016) reported a significant difference in depression between participants suffering from moderate/severe neuropathic pain to participants with no/mild neuropathic pain; and one study (Wickramasinghe et al., 2016), found that that depression among DPN participants was higher than in those without DPN.

Table 9: Outcomes associated with RCTs of psychological interventions

Study	Intervention outcome/Psychosocial variable	Comparison	Cohen's d (95% CI)	Correlation r (95% CI)	Magnitude Interpretation	P value
Otis et al. (2013)	CBT (posttreatment) -Depression	Between-group	0.68 (-0.19 to 1.55)	-	Medium	>0.05
	CBT (follow-up) - Depression	Between-group	0.47 (-0.39 to 1.33)	-	Small	>0.05
	CBT (posttreatment) - Pain	Between-group	0.91 (0.02 to 1.8)	-	Large	>0.05
	CBT (follow-up)-Pain interference	Between-group	0.85 (-0.03 to 1.74)	-	Large	>0.05
	CBT (posttreatment)- Pain Severity	Between-group	0.88 (-0.01 to 1.77)	-	Large	>0.05
	CBT (follow-up)- Pain Severity	Between-group	0.83 (-0.05 to 1.71)	-	Large	>0.05
Teixeira, (2010)	Mindfulness-QOL	Between-group	-0.16 (-1.1 to 0.78)	-	Small	>0.05
	QoL and Sleep	Whole sample	-	0.53 (0.048 to 0.813)	Large	<0.05
Pfammatter, (2010)	TB-Pain Severity/Control (Session 1)	Whole sample	-	-0.42 (-0.721 to 0.014)	Large	>0.05
	TB-Pain Severity/Control (Session 4)	Whole sample	-	-0.62 (-0.830 to -0.257)	Large	<0.05
	TB-Pain Severity/Control (Session 6)	Whole sample	-	-0.65 (-0.845 to - 0.303)	Large	<0.01

Note: QOL: Quality Of Life, Correlation r: Correlation coefficient, "-": not applicable, TB: Thermal Biofeedback, CI: Confidence Interval

3.6 Anxiety and Pain Outcomes

Five cross-sectional studies investigated anxiety in relation to pain severity and pain interference (Bouhassira et al., 2013; Gore et al., 2005; Hoffman et al., 2009; Selvarajah et al., 2014; Themistocleous et al., 2016) (Table 10). One study (Selvarajah et al., 2014) investigated the association between anxiety and pain in patients with confirmed PDN differing in pain intensity and found a medium effect size; and one study (Gore et al., 2005) found a large effect size, between patients with mild and severe PDN. However, contrary to this, another study (Hoffman et al., 2009) demonstrated an overall weak and negative effect size between anxiety and pain severity. This appeared to be due to unexpected high anxiety reported in some of their low pain participants, otherwise the trend was for those reporting severe pain to also report higher anxiety.

Two further studies also investigated anxiety in relation to pain outcomes, but data were not available to compute the effect sizes. One study (Bouhassira et al., 2013) reported that participants with chronic pain and neuropathic characteristics had higher anxiety scores compared to those without neuropathic pain, and one study (Themistocleous et al., 2016) investigated pain-related anxiety and found that participants with moderate/severe neuropathy reported significantly higher scores compared to participants with mild/no neuropathy.

3.7 Sleep and Pain Outcomes

Seven cross-sectional studies examined the association between sleep and pain in PDN (Bouhassira et al., 2013; Gore et al., 2005; Hoffman et al., 2009; Jacovides et al., 2014; Selvarajah et al., 2014; Wickramasinghe et al., 2016; Zelman et al., 2006) (Table 10). Two studies reported large effect sizes. In the first study participants were grouped according to pain severity and a strong association between pain severity and sleep impairment was found (Gore et al., 2005). These findings were supported by a more recent study which reported a large effect between pain and sleep interference

(Jacovides et al., 2014). One study found a medium effect when comparing individuals with PDN and the general US population. Whereas, another study (Hoffman et al., 2009), found a small effect between sleep and pain.

Three studies also investigated the relation between sleep disturbances and pain but data were not available to compute the effect sizes. One study (Bouhassira et al., 2013) reported that participants with neuropathic pain had more sleep disturbance than participants without neuropathic pain. One study (Themistocleous et al., 2016) showed significantly greater sleep impairment in participants with moderate/severe neuropathy relative to those with mild/no neuropathy. One study (Wickramasinghe et al., 2016), concluded that 43.7% of the total sample had sleep disturbances due to their neuropathic symptoms.

3.8 Catastrophic Thinking and Pain Outcomes

Two cross-sectional studies (Selvarajah et al., 2014; Themistocleous et al., 2016) and one prospective cohort (Mai et al., 2015) examined pain catastrophizing (Table 10). It is worth noting that there are three dimensions within catastrophizing: rumination, magnification, and helplessness (Sullivan, Bishop, & Pivik, 1995). One study showed that helplessness and rumination are strongly associated with the experience of pain in diabetic neuropathy (Selvarajah et al., 2014). In another study, participants with moderate/severe PDN scored significantly higher on catastrophizing than those with no/mild PDN (Themistocleous et al., 2016). Finally, in one study catastrophizing did not predict outcome, possibly because the sample size was relatively small (N=60) (Mai et al., 2015). None of the studies described provided adequate data to compute effect sizes.

3.9 Other Psychosocial Variables and Pain Outcomes

One study investigated the association between acceptance of illness and QOL finding a large effect size (Lewko et al., 2007) (Table 10). One study, of prospective cohort design study, investigated

depression as an outcome variable at 18 months and found that this was predicted by increased pain from baseline to nine months (Vileikyte et al., 2009). Another study investigated the association between acceptance of pain, and anxiety and depression. The results demonstrated that lower acceptance scores were strongly associated with higher levels of depressive symptoms and anxiety. However, the data was insufficient to calculate an effect size (Selvarajah et al., 2014).

One study investigated the role of a number of different fears, including fear of movement (kinesiophobia), fear of fatigue, fear of hypoglycaemia, fear of pain, fear of falling, and fear of negative evaluation, in relation to QOL. This study found medium to large correlations between QoL and these fear-related variables (range: r=0.39 to r=0.71). This study also found medium to large correlations between fear-related variables and disability (range: r=0.28 to 0.66) (Geelen et al., 2017).

3.10 Pain and Quality of Life

Most of the studies included in this review (20/27) aimed to capture the perceived impact of PDN on QOL (Table 10). These studies were mainly cross-sectional and mostly concluded that pain is associated with reduced QOL. The factors framed as predictors of QOL, or independent variables, include presence of pain, pain intensity and pain severity. However, it is also possible to conceive QOL as a potential contributory psychosocial factor in relation to other pain-related outcomes. Indeed, common QOL measures often incorporate items assessing psychological functioning, such as depression and anxiety, as well as usual daily activities (EQ-5D-5L) (Van Reneen & Oppe, 2015).

Eight studies provided sufficient data to calculate effect sizes, reflecting mostly large associations between QOL and pain. Six studies found large effects in comparisons between groups with severe versus mild PDN (Bouhassira et al., 2013; Geelen et al., 2016; Sadosky et al., 2013; Zelman et al., 2005). One study found a medium and negative effect between pain severity and QOL (Levterova et al., 2018). And another study found a small effect between pain severity and QOL (Hoffman et al.,

2009). Twelve additional studies reported negative associations between QOL and pain but did not provide enough information to calculate effect sizes (AL-Mahmood et al., 2018; Benbow, 1998; Bouhassira et al., 2013; Galer et al., 2000; Kulkantrakorn & Lorsuwansiri, 2013; Mai et al., 2015; Selvarajah et al., 2014; Themistocleous et al., 2016; Tölle et al., 2006; Van Acker et al., 2009; Wickramasinghe et al., 2016; Zelman et al., 2005).

Table 10: Associations between depression, anxiety, QOL, sleep and pain outcomes for studies reporting sufficient data to compute effect sizes

Studies	Comparison	Study Design	Type of analysis*	Pain/Neuropathy outcome (Assessment)	Psychosocial Assessment	Cohen's d (95% CI)	Correlation r (95% CI) or β if only multivariate regression	Magnitude of Relation/ Effect	P value	Proportion of Significance
Depression										
Dobrota et al. (2014)	Between-group	Cross-Sectional	Univariate	Presence of Pain (VAS, LANSS)	BDI	1.07 (0.73 to 1.4)	-	Large	<0.001	-
Gore et al. (2005;2006)	Between-group	Cross-Sectional	Univariate	Pain Severity (BPI)	HADS-D	0.99 (0.66 to 1.32)	-	Large	<0.001	-
Hoffman et al. (2009)	Between-group	Cross-Sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	HADS-D	0.02 (-0.51 to 0.55)	-	Weak	N/R	1/3
Selvarajah et al. (2014)	Within-group	Cross-Sectional	Multivariate (reported *r* is univariate analysis)	Pain Intensity (NPS)	HADS-D	-	0.33 (0.161 to 0.480)	Medium	<0.01	-

Vileikyte et al. (2005)	Within-group	Cross-Sectional	Multivariate	Pain Severity (NeuroQoL)	HADS-D	-	Pain predicting depression β =-0.27 (0.185 to 0.351)	Small	<0.001	-
Vileikyte et al. (2009)	Baseline-Follow up	Longitudinal (change in pain predicting follow-up depression)	Multivariate	Pain Severity (NeuroQoL)	HADS-D	-	Pain intensity predicting depression β =-0.04 (-0.146 to 0.067)	Weak	< 0.05	-
							Pain disability predicting depression β =0.16 (0.054 to 0.262)		<0.01	
Anxiety										
Gore et al. (2005;2006)	Between-group	Cross-Sectional	Univariate	Pain Severity (BPI)	HADS-A	0.97 (0.64 to 1.29)	-	Large	<0.001	-
Hoffman et al. (2009)	Between-group	Cross-Sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	HADS-A	-0.15 (-0.68 to 0.18)	-	Weak	N/R	2/3

Selvarajah et al. (2014)	Within-group	Cross-Sectional	Multivariate (reported *r* is from univariate analysis)	Pain Intensity (NPS)	HADS-A	-	0.45 (0.295 to 0.582)	Medium	<0.01	-
Pain/diabetes-related fears										
Geelen et al. (2017)	Within group	Cross-Sectional	Multivariate	Pain Severity and Disability (VAS, PDI)	HFS, TSK, PASS-20, FES-I, TSF, BFNE	-	0.78 [a] (0.695 to 0.73 [a] (0.635 to 0.796)	Large	N/R	3/11
Quality of life										
Dobrota et al. (2014)	Between-group	Cross-Sectional	Univariate	Pain Presence (VAS, LANSS)	SF-36	-1.12 (-1.45 to -0.78)	-	Large	<0.001	-
Geelen et al. (2017)	Within group	Cross-Sectional	Multivariate (reported *r* is from univariate analysis)	Pain Severity and Disability (VAS, PDI)	QOL-DN	-	0.49 (0.348 to 0.610)	Large	<0.01	-
Gore et al. (2005;2006)	Between-group	Cross-Sectional	Univariate	Pain Severity (BPI)	EQ-5D	-1.96 (-2.34 to -1.58)	-	Large	<0.01	-

Hoffman et al. (2009)	Between-group	Cross-Sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	EQ-5D VAS	-0.12 (-0.64 to 0.41)	-	Small	<0.05	-
Jacovides et al. (2014)	Between-group	Cross-Sectional	Univariate	Pain Presence (DN4)	EQ-5D	-0.95 (-1.1 to -0.81)	-	Large	N/R	-
Levterova et al. (2018)	Between-group	Cross-Sectional	Univariate	Pain Presence (DN4)	SF-36v2	-0.5 (-2.13 to 1.13)	-	Medium	N/R	4/8
Lewko et al. (2007)	Within-group	Cross-sectional case-control	Univariate	Presence of diabetic peripheral neuropathy (assessment of neuropathy unclear)	SF-36v2, AIS	-	0.48 (0.256 to 0.656)	Large	<0.05	-
Sadosky et al. (2013)	Between-group	Cross-Sectional	Univariate	Pain Severity (BPI-SF)	SF-12v2	-1.49 (-2.11 to -0.86)	-	Large	<0.001	-
Zelman et al. (2005)	Between-group	Cross-Sectional	Univariate	Severity (BPI, VRS)	EQ-5D	-15.69 (-17.44 to -13.89)	-	Large	<0.001	-

Zelman et al. (2005)	Between-group	Cross-Sectional	Univariate	Severity (BPI, VRS)	SF-12v2	-1.09 (-1.42 to 0.76)	-	Large	<0.001	-
Sleep										
Gore et al. (2005;2006)	Between-group	Cross-Sectional	Univariate	Pain Severity (BPI)	MOS	1.46 (1.11 to 1.8)	-	Large	<0.001	-
Hoffman et al. (2009)	Between-group	Cross-Sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	MOS	0.31 (-0.22 to 0.84)	-	Small	<0.05	-
Jacovides et al. (2014)	Between-group	Cross-Sectional	Univariate	Pain Presence (DN4)	DSIS	1.12 (0.98 to 1.27)	-	Large	N/R	-
Zelman et al. (2006)	Between-group (Cohen's d)/ Within-group (β)	Cross-Sectional	Multivariate	Severity (BPI-DN)	MOS	0.47 (0.33 to 0.61)	Pain predicting sleep problems: β =0.30 (0.184 to 0.408)	Medium	<0.001	-

Note: "-": not applicable. Only groups of absolute interest are reported in this table, [a]: The effect size reported is not originally calculated by the author of the study but by the first author of this systematic review. AIS: Acceptance of Illness Scale, BDI: Beck Depression Inventory, BFNE: Brief Fear of Negative Evaluation Scale, CI: Confidence Interval, DN4: Douleur Neuropathique 4, DSIS: Daily Sleep Interference Scale, EQ-5D: EuroQol, FES-I: Falls Efficacy Scale-International, HADS: Hospital Anxiety and Depression scale, HFS: Hypoglycaemia Fear Survey, LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, mBPI: modified Brief Pain Inventory, MOS: Medical Outcomes Study-sleep scale, MPQ: McGill Pain Questionnaire, NDS: Neuropathy Disability Score, NPS: Neuropathic Pain Scale, NeuroQol: Neuropathy and Foot Ulcer-specific Quality of Life Instrument, N/R: not reported, PASS-20: Pain Anxiety Symptom Scale, PDI: Pain Disability Index, P value: In instances where an effect size is calculated for a number of different subscales with different P values, a proportion of significance is reported as the number of comparisons of the total comparisons that reported a significant difference. QOL-DN: Norfolk Quality of Life Questionnaire, r: correlation coefficient effect size or otherwise explained in the comments, SF-12v2: Short Form Health Survey Version 2, SF-36: Short Form Health Survey, TSF: Tampa Scale of Fear of Fatigue, TSK: Tampa Scale of Kinesiophobia, VAS: Visual Analogue Scale, VRS: Verbal Rating Scale. For papers which had three or more groups based on pain severity, the comparison was undertaken between the group with the least severe symptoms and the most severe symptoms. *When both univariate and multivariate analyses were reported in the same paper, we extracted univariate data given differences in multivariate models across study which limit their interpretability. Where only a multivariate model was reported, this data was extracted.

3.11 Quality Assessment

The inter-rater reliability (IRR) in assessing the quality of the twenty-seven included studies was good, at 87.5% agreement between the two reviewers. There were some minor disagreements, mainly regarding the internal validity of the studies, but these were solved without consulting another member of the research team.

Overall, the methodological quality score, using the Downs and Black (1998) quality assessment tool, was high in 14 studies (AL-Mahmood et al., 2018; Bouhassira et al., 2013; Currie et al., 2006; Dobrota et al., 2014; Galer et al., 2000; Geelen et al., 2017; Gore et al., 2005; Hoffman et al., 2009; Levterova et al., 2018; Selvarajah et al., 2014; Van Acker et al., 2009; Vileikyte et al., 2005; Vileikyte et al., 2009; Wickramasinghe et al., 2016), medium in four studies (Mai et al., 2015; Sadosky et al., 2013; Themistocleous et al., 2016; Zelman et al., 2005) and low in five studies (Benbow, 1998; Jacovides et al., 2014; Lewko et al., 2007; Kulkantrakorn, & Lorsuwansiri, 2013; Tölle et al., 2006). Most common reasons for these studies losing points in the scoring was the External Validity component and Internal Validity-Confounding (selection bias) component (see Table 9).

Table 11: Methodological quality of observational studies (Downs & Black, 1998)

Study	Component Score: A	Component Score: B	Component Score: C	Component Score: D	Overall Score
AL-Mahmood et al. (2018)	5	2	3	2	92.3% (12/13)
Benbow (1998)	4	1	0	1	46.2% (6/13)
Bouhassira et al. (2013)	5	2	3	2	92.3% (12/13)
Currie et al. (2006)	6	0	3	2	84.7% (11/13)
Dobrota et al. (2014)	5	2	3	2	92.3% (12/13)
Galer et al. (2000)	5	2	2	1	71.4% (10/14)
Geelen et al. (2016; 2017)	4	1	3	0	66.7% (8/12)
Gore et al. (2005; 2006)	6	0	2	0	57.1% (8/14)
Hoffman et al. (2009)	6	0	3	2	84.7% (11/13)
Jacovides et al. (2014)	5	0	2	0	50% (7/14)
Kulkantrakorn & Lorsuwansiri, (2013)	4	0	0	1	38.5% (5/13)
Levterova et al. (2018)	5	2	3	2	92.3% (12/13)
Lewko et al. (2007)	3	0	1	1	38.5% (5/13)
Mai et al. (2015)	4	0	2	2	57.1% (8/14)
Sadosky et al. (2013)	5	0	3	0	61.5% (8/13)
Selvarajah et al. (2014)	5	1	3	1	77% (10/13)
Themistocleous et al. (2016)	5	0	3	0	61.5% (8/13)
Tölle et al. (2006)	5	0	1	0	46.2% (6/13)
Van Acker et al. (2009)	5	2	3	2	92.3% (12/13)
Vileikyte et al. (2009)	5	1	3	2	78.6% (11/14)
Vileikyte et al. (2005)	5	1	3	2	84.7% (11/13)
Wickramasinghe et al. (2016)	5	1	3	1	77% (10/13)
Zelman et al. (2005)	6	0	2	0	57.1% (8/14)
Zelman et al. (2006)	6	0	2	0	57.1% (8/14)

Note: Component Score **A**: Reporting, score range 0-7, Component Score **B**: External Validity, score range 0-2, Component Score **C**: Internal Validity-Bias, score range 0-3,

Component Score **D**: Internal Validity-Confounding (selection bias), score range 0-2

The three RCTs were assessed with the Cochrane risk of bias tool, which showed that one study had low risk of bias (Otis et al., 2013), one study had unclear risk of bias (Teixeira, 2010) and the last had high risk of bias (Pfammatter, 2010). The studies were more likely to have low risk of bias for random sequence generation and high risk of bias in potential for selective reporting and "other" bias. More details on the quality assessment of the studies can be found in Tables 11, 12 and Figure 13.

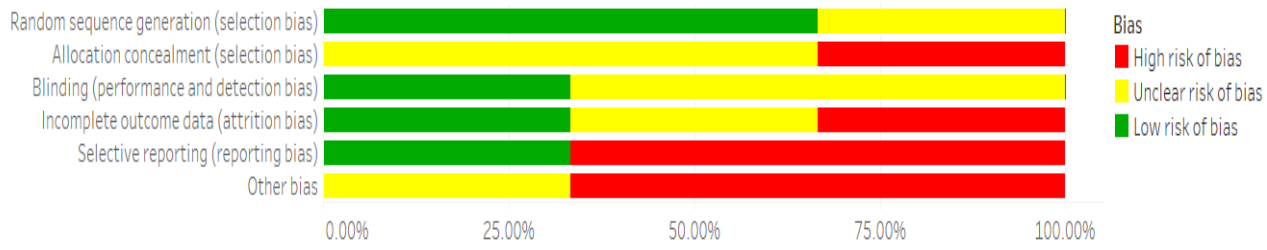

Figure 13: Quality of RCTs - Cochrane's Risk of Bias assessment tool

4. Discussion and conclusions

This systematic review was specifically focused on evidence for the role of psychosocial factors and related treatments in relation to outcomes in PDN. The relevant literature was heterogeneous and included few randomised-controlled trial designs. The search revealed twenty-seven studies (twenty-nine papers). These provide limited evidence of mixed quality for benefits from psychological interventions, and some high-quality evidence for associations between depression, anxiety, sleep, and QOL, typically in relation to pain in PDN. There was less evidence for other outcomes, such as physical, social, or emotional functioning. The results of this review identify a need for the further investigation of psychosocial processes in PDN, in relation to a wider set of clinical outcomes, guided by a clear theoretical model, and for theory-driven treatment development evaluated in larger RCTs.

The identification of only three small RCTs in the review limits the conclusions that can be drawn about the potential efficacy of psychosocial treatment for PDN. These were very small in size, included three distinctly different types of treatment and produced inconsistent results. The limited number of RCTs of psychological treatments for PDN contrasts the larger number of reasonably higher quality RCTs for chronic pain in general, estimated at 40 (Eccleston et al., 2015) and in conditions such as fibromyalgia where there are currently around 29 RCTs of CBT (Bernardy et al., 2018). Notably, the lack of trials identified in the current review is consistent with a review of RCTs of psychological treatments for neuropathic pain (not restricted to PDN) (Eccleston et al., 2015). Unfortunately, the current evidence from these studies is not sufficient to support specific recommendations regarding effective psychological treatment for PDN.

Current results provide limited clues regarding the types of psychosocial factors that might influence outcomes in PDN, and almost exclusively included psychological factors and not social ones. With the exception of fear of negative evaluation, a clear social factor (Geelen et al., 2017), and a study of changing social perception (Vileikyte et al., 2009), none of the commonly studied social factors (e.g. social support, spouse responses), often found to relate to chronic pain, were featured in the available evidence here.

This review found evidence of a mostly consistent positive association between depression and the presence, intensity or severity of pain in people with PDN, with effects ranging from small to large. This is consistent with a large body of findings in the wider chronic pain literature that persistently links depression and chronic pain outcomes and depressive symptoms with diabetes (Anderson et al., 2001; Banks & Kerns, 1996; Moreira, Amancio, Brum, Vasconcelos, & Nascimento, 2009; Rayner et al., 2016; Velly et al., 2011). Within the current review, the majority of the studies were cross-sectional, which precludes statements about the direction of association between these variables. Drawing on the wider literature, it is likely that there is a bi-directional association between pain and

depression. Current results are also consistent with results from a meta-analysis of 27 studies investigating depression in diabetic patients that also showed a significant correlation between depression and complications of diabetes (De Groot et al., 2001).

Another key finding arising from this review was the positive association, ranging from medium to large effects, between anxiety and pain severity or intensity. Only one of five studies found an inconsistent effect. This overall result is consistent with the broader chronic pain literature where anxiety is found to either contribute to, or reflect effects of, poor functioning and health (Kroenke et al., 2013). Anxiety and depression are often highly correlated when measured simultaneously in the same sample. The degree to which the present findings for these variables reflect significantly distinct processes and targets for change is unclear (McCracken & Morley, 2014; Turk, Audette, Levy, Mackey, & Stanos, 2010).

Some of the most frequently studied variables in the context of chronic general or musculoskeletal pain include catastrophizing and acceptance (Quattrini & Tesfaye, 2003; Sugiura & Sugiura, 2016). Here, in contrast, only three studies included catastrophizing and two studies examined some form of acceptance. Overall, these studies did not provide a clear basis for inferring the size of the association or potential utility of either of these variables for guiding treatment development for PDN. Only one study (two papers) investigated the relationship between pain-related fears and pain. This study showed a large, positive association between various fears, including fears of pain, hyperglycaemia, falling, fatigue, with increased neuropathic disability, reduced QOL and pain intensity. This was, as far as we are aware, the first study aiming to specify pain-related fears in PDN population. The fact that there is only one study of fear in relation to PDN may appear surprising as the Fear-Avoidance Model is otherwise a widely applied and productive model of disability in chronic pain in general (Boselie & Vlaeyen, 2017; Leeuw et al., 2007a; Vlaeyen, de Jong, Geilen, Heuts, & van Breukelen, 2002). All of these anxiety-related variables overlap, to a degree, conceptually and in

their measurement. This again can point to the need for conceptual clarity in the choice of variables we investigate.

Evidence of medium to large associations was also found between pain and sleep disruption in the present systematic review, based on three studies. This may be a potentially useful relation as poor sleep appears common in individuals with neuropathic pain in general and with PDN in particular (Quattrini & Tesfaye, 2003; Zelman et al., 2006). Poor sleep in the context of chronic pain appears potentially modifiable (Daly-Eichenhardt, Scott, Howard-Jones, Nicolaou, & McCracken, 2016; Tang et al., 2015) and is a target that could guide treatment development.

The majority of the studies reviewed included QOL. Predominantly these studies focused on the impact of the disease, designed to document the impact of PDN on QOL. Most studies found large associations between pain and poor QOL. This is not surprising and in fact both direct adverse impacts of PDN on QOL, and indirect impacts from depression and anxiety in the context of PDN, are well documented (Gormsen, Rosenberg, Bach, & Jensen, 2010; Grandy, Chapman, & Fox, 2008; Schram et al., 2009; Svendsen, Jensen, Hansen, & Bach, 2005). The reason that, in a sense, we have turned QOL around and conceived it as a potential influence on other outcomes in PDN, is that we feel that components of QOL, particularly the more behavioural components, such as social and physical activities, are essentially directly modifiable. We know from general chronic pain studies that it is possible to take a direct approach to improving daily activities, for example, and achieve both improvements in these activities and in such outcomes as pain, depression, and other symptoms at the same time (Hann & McCracken, 2014).

It is notable that there were three additional studies of biofeedback identified during the literature search (Fiero, Galper, Cox, Phillips, & Fryburg, 2003; Pataky et al., 2009; Rodriguez et al., 2013). However, the reported treatment outcomes were physiological, for example temperature reduction, rather than reports of pain intensity, pain-related functioning, or psychological distress. Hence these

studies were excluded from this systematic review. Thus, future studies exploring biofeedback in this context might benefit from including measures of pain and functioning as outcomes.

Overall, setting aside QOL as a direct treatment target, available evidence reveals that few modifiable psychosocial factors have been studied in the literature of PDN. Also, when they are studied, they are generally examined in relation to pain as an outcome, and not in relation to a wider range of outcomes, such as physical, social, or emotional functioning. In this systematic review, variables like anxiety, depression and QOL are treated as both outcomes and correlates of outcome. A few studies examined correlations with these variables, except for pain, pain severity, pain interference, and acceptance of pain. Most of the studies include anxiety and depression as potential independent variables. Only six studies, all cross-sectional, examined such otherwise frequently studied variables as catastrophizing, fear, or acceptance. What seems to be entirely missing are studies of conventional variables such as beliefs or coping (Eccleston et al., 2015) or other facets of psychological flexibility (McCracken & Morley, 2014). Hence, results, as they stand, do not identify specific psychosocial factors or treatment methods that ought to be targeted or applied in PDN, nor do they appear to provide clear guidance for treatment development, other than to highlight the potential role of emotional functioning, sleep, and perhaps a direct approach to daily functioning. The very limited studies of psychological treatments or psychosocial factors in PDN compared to other chronic pain conditions, particularly in the context of the clear treatment needs in PDN, raises question as to why this is the case, and what might be the barriers to psychological studies in this population.

Several limitations of this systematic review need to be considered. Our defined population was explicitly adults, therefore, the results of this review cannot be generalised to children and adolescents. We used broad search terms for PDN, psychosocial factors and psychological interventions to identify all the eligible studies; however, given the broad nature of the search, it is

possible that we may have missed studies. We calculated effect sizes based on the given mean and SDs, but not all studies provided sufficient data for effect sizes. We collapsed multiple between-groups analyses into dichotomous comparisons to enable comparison across studies to minimise paired comparisons; however, this may have eliminated a more subtle understanding of the association between psychosocial factors and pain outcomes.

Future research is encouraged to examine a wider array of theoretically-based psychosocial factors than currently done and to more deeply pursue the utility of such current theoretical models as Fear Avoidance Model and Psychological Flexibility model. Naturally, studies from either of these models can incorporate the role of emotional functioning, and ought to do so, as this domain is the one that is most clearly highlighted here as relevant, and it appears that the Psychological Flexibility Model can address sleep (Daly-Eichenhardt et al., 2016; McCracken, Williams, & Tang, 2011).

There appears to be a clear potential for non-pharmacological, particularly psychological treatments, for PDN. The current review does not, however, clarify specific psychological processes to target, certainly not comprehensively. The absence of fully powered, high-quality studies of psychological treatment for PDN found here is notable. Future trials may explore questions around non-participation and drop-out and ways to enhance access and acceptability in addition to the core questions of effectiveness. It is recommended that future treatments aim not only to treat pain but also improve other aspects of the condition, such as emotional and physical functioning, and participation in life in general. The challenge here then seems to be the identification of a model of treatment processes with the potential to produce these general results

Table 12: Methodological quality of the RCTs (Cochrane risk of bias assessment tool)

	Random sequence generation (selection	Allocation concealment	Blinding (performance and detection bias)	Incomplete outcome data	Selective reporting	Other bias
Otis et al. (2013)	+	?	+	+	+	?
Pfammatter, (2010)	?	-	?	-	-	-
Teixeira, (2010)	+	?	?	?	-	-

Low risk of bias

Unclear risk of bias

High risk of bias

Acknowledgments

K.K., first author, responsible for the work as a whole, contributed to the design of the project, searched the selected databases, screened the titles, selected the eligible articles, did the data extraction and methodological quality check, interpreted the results, and produced the first draft of the manuscript. L.M. contributed to the conception and research plan, to the final selection of the articles, critically revised the manuscript and approved the final version. K.W. contributed to the design of the study, to the final selection of the articles, critically evaluated the manuscript and approved the final version. W.S. acted as the second reviewer of the research and contributed to the data extraction and methodological quality check. S.K. acted as a third reviewer, contributed to the search of the databases, screening of the titles and abstracts, selection of the eligible articles, data extraction and quality assessment. All authors contributed to critically revising the manuscript, and approved the final submitted version. None of the authors declares a conflict of interest or any financial or other relationship that might lead to any conflict.

3.3 Summary

This chapter describes a systematic review aiming to identify psychosocial factors associated with PDN through survey studies and treatment trials. We identified 24 observational studies and 3 treatment trials. Key results suggested that depression, anxiety, sleep and quality of life are the most studied variables in relation to pain outcomes in PDN, each demonstrating consistently predictable associations mostly in relation to pain in PDN.

Chapter 4: The Application of Psychological Flexibility and Acceptance and Commitment Therapy (ACT) in Adults with Painful Diabetic Neuropathy: A Cross-Sectional Survey

4.1 Chapter Overview

As discussed in chapter 2, there is a growing body of evidence supporting the acceptability and efficacy of ACT in people with chronic pain. Likewise, a growing number of studies have examined particular treatment processes within the PF model including acceptance, committed action, cognitive fusion, self as a context, and values in chronic pain. However, only two studies (Lewko et al., 2007; Selvarajah et al., 2014) have measured pain acceptance in PDN and no studies have investigated other PF processes or evaluated the applicability of the PF model and the potential suitability of ACT in people with PDN. This chapter aims to examine the role of PF in people with PDN and whether ACT is potentially relevant for this population via a cross-sectional survey.

This chapter is published in the following article at The Journal of Contextual Cognitive Behavioral Science (Appendix Q):

Kioskli, K., Winkley, K., & McCracken, L. M. (2019). Might psychological flexibility processes and Acceptance and Commitment Therapy (ACT) apply in adults with painful diabetic neuropathy? A cross-sectional survey. *The Journal of Contextual Cognitive Behavioral Science. 13*(2019), 66-73.

Chapter naming and numbering are presented as they are in the published article.

4.2 Published Article

Manuscript Number: JCBS_2019_37

Title: Might psychological flexibility processes and Acceptance and Commitment Therapy (ACT) apply in adults with painful diabetic neuropathy? A cross-sectional survey

Article Type: Research Article

Corresponding Author: Lance M McCracken, PhD

Corresponding Author's Institution: King's College London

Authors: Kitty Kioskli, MSc; Kirsty Winkley, PhD

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Conflicts of interest: None declared.

Note: This is the authors' accepted copy.

Highlights:

- Psychological Flexibility is thought to contribute to processes of pain, emotional experiences, and daily activities.
- Pain severity is associated with psychological functioning for people with Painful Diabetic Neuropathy.
- Psychological Flexibility components may improve psychological treatments for people with PDN.

Abstract

Painful diabetic neuropathy (PDN) is a distressing and disabling condition. There is, surprisingly, relatively little research into the role of psychological variables related to PDN. The aim of this study was to investigate the association between psychological flexibility, daily functioning, and distress in people with PDN. This cross-sectional study included 225 participants who were recruited from hospital services and online. In correlation analyses, acceptance of pain was shown to be negatively correlated with pain intensity ($r=-0.21$, $p<0.01$), pain distress ($r=-0.25$, $p<0.01$), functional impairment ($r=-0.38$, $p<0.01$), depression severity ($r=-0.41$, $p<0.01$), and depression impact ($r=-0.41$, $p<0.01$). Cognitive fusion correlated positively with pain intensity ($r=0.14$, $p<0.05$), functional impairment ($r=0.24$, $p<0.01$), depression severity ($r=0.44$, $p<0.01$), and depression impact ($r=0.20$, $p<0.01$). Committed action correlated negatively with functional impairment ($r=-0.22$, $p<0.01$), depression severity ($r=-0.43$, $p<0.01$), and depression impact ($r=-0.21$, $p<0.01$). In regression analyses, the four variables representing psychological flexibility accounted for significant variance in all the equations except in the case of pain distress. However, in some cases the variance accounted for was less than that accounted for by pain intensity. For example, in the equation for functional impairment, pain intensity accounted for 32.2% of the variance, while psychological flexibility accounted for 6.8% of the variance. These results suggest that psychological flexibility may play a smaller role, relative to pain intensity, in the context of PDN as compared to the larger populations of chronic, mostly musculoskeletal, pain. The reliability and generalisability of these results need to be established.

Key Words: painful diabetic neuropathy; cross-sectional survey; psychological flexibility; Acceptance and Commitment Therapy

1. Introduction

The World Health Organization (WHO, 2016) estimates that approximately 422 million adults live with diabetes mellitus (DM) worldwide. If DM is poorly managed, it can lead to complications, such as kidney failure, heart disease, stroke, blindness and neuropathy. The most common type of neuropathy caused by DM is painful diabetic neuropathy (PDN), affecting 25-30% of people with DM (Daousi et al., 2004; Davies, Brophy, Williams, & Taylor, 2006; Geelen et al., 2017). PDN is a complex condition affecting the peripheral nervous system (Treede et al., 2007), resulting in loss of sensation, numbness, and a burning, sharp, electrical, stinging pain in the affected area, which often worsens at night (Bouhassira et al., 2005; Daousi et al., 2004; Davies et al., 2006; Geelen et al., 2017). It is known to negatively affect physical and mental health, to reduce overall quality of life (Benbow, 1998; Fernando et al., 2013; Galer et al., 2000; Gore et al., 2005; Van Acker et al., 2009; Vileikyte et al., 2009), and to impact work, social life, general activities, and sleep (Geelen et al., 2017). There are few studies of the role of psychological processes in people with PDN (Kioskli et al., 2019) and these have focused on a narrow set of variables, such as depression and anxiety (Gore et al., 2005), and fears (Geelen et al., 2017).

Forms of cognitive behavioural therapy (CBT) are the most often used psychological treatments for chronic pain. These include contextual forms of CBT, such as Acceptance and Commitment Therapy (ACT) (Hayes et al., 1999; McCracken & Morley, 2014; McCracken & Vowles, 2014). ACT is a form of CBT that includes methods of acceptance, mindfulness and behaviour change (Hayes et al., 2003) and explicitly focuses on increasing psychological flexibility (PF; Hayes et al., 2011). PF is a model of wellbeing and performance that includes six related processes: acceptance, cognitive defusion, present moment awareness, self-as-context, values, and committed action (Hayes et al., 2006). This is sometimes referred to as a focus on openness to experiences, awareness of the present moment, and engagement in actions that are guided by values and goals (Hayes et al., 2011). The current

literature indicates that ACT and closely allied approaches are at least as effective as other psychological approaches for managing chronic pain (Hann & McCracken, 2014).

Current treatment options for PDN are mainly pharmacological. There are only four RCTs of psychological treatments for PDN, including CBT, mindfulness, mindfulness-based stress reduction (MBSR) and thermal biofeedback assisted relaxation (Otis et al., 2013; Nathan et al., 2017; Pfammatter, 2010; Teixeira, 2010). The results from the mindfulness study (Teixeira, 2010) suggested a small between-group effect in the mindfulness group on quality of life (*d*=-0.16, 95% CI: -1.1 - 0.78) and large effect on sleep (*r*= 0.53, 95% CI: 0.048 - 0.813). No significance was speculated. Evidence from the biofeedback study (Pfammatter, 2010) did not produce any statistically significant results. The CBT study (Otis et al., 2013), an RCT (N=20), showed significant decreases in pain severity and pain interference in the CBT group, at post-treatment and follow-up (*d*= 0.83-0.91), compared to the control group. Results from the MBSR study (Nathan et al., 2017) showed that more than half of participants in the experimental group (19/30) improved in depression, pain interference, quality of life, catastrophizing and function. Overall, their results are promising and, at the same time, due to small sample sizes or small effects, show no clear evidence-based psychological approach for PDN.

Previous studies of chronic pain provide support for the role of PF in relation to well-being and daily-functioning, in people with mixed chronic musculoskeletal pain conditions, (McCracken, Gauntlett-Gilbert, & Vowles, 2007; Vowles, McCracken, & Eccleston, 2008; McCracken & Velleman, 2010) chronic low back pain (Mason, Mathias, & Skevington, 2008), and fibromyalgia (Yu, Norton, Almarzooqi, & McCracken, 2017). Preliminary evidence of this type has led in turn to successful treatment trials of ACT in these conditions (Hann & McCracken, 2014). We simply do not know whether the results from studies of PF in the context of chronic musculoskeletal pain will be replicated in the context of PDN, again, a condition for which there are very few psychological studies, and none focused on PF.

The complex and particularly intractable qualities of PDN are important as motivators for research into the role of PF. The prospects for pain control are practically very limited, even when compared to other pain conditions, and hence an approach that supports the capacity to function without pain control, and in the midst of multiple co-morbid symptoms, appears relevant to this condition. However, no published studies have yet explored either the suitability of ACT or the applicability of PF to individuals with PDN.

Finally, there is one more motivation for the study of PDN in a context of many studies of other pain conditions. It appears that neuropathic pain conditions in clinical practice are implicitly mainly regarded as mainly a physical problem with relatively little psychological input (Kioskli et al., 2019), possibly because that pathology underlying the pain appears undeniable. This conclusion is supported by evidence from large cohorts of people seeking specialty treatment for chronic pain where few, if any, report diagnosis of neuropathic pain (Mason et al., 2008; McCracken & Velleman, 2010; Yu et al., 2017). We argue that, in order to overcome this bias against access to psychosocial thinking and treatment development for PDN, evidence for the role of psychological factors must be shown in this condition specifically.

Neuropathic pain has different physiology from non-neuropathic pain, otherwise called nociceptive pain. This distinction is also sometimes called pathophysiological versus physiologic (Akter, 2019). Neuropathic pain is caused by damage to either the central or the peripheral nervous system or both. This type of pain is generally never useful for the individual - it never serves a useful purpose, such as to warn about a potential injury or to support healing. Also, neuropathic pain is more likely to be chronic. The basic characteristics of nociceptive or physiologic pain are that it is caused by activation of nociceptors, alerts the individual in order to avoid injury and passes over time (Pasero, 2004). Even though there are a large number of studies examining psychosocial factors in general pain conditions that are predominantly nociceptive this is not the case for neuropathic pain.
The purpose of the present study is to survey people with PDN and examine the role of PF in relation

to their daily functioning, including emotional functioning. Our research question is whether PF, here including acceptance, cognitive defusion, committed action, and self-as-context, is relevant and potentially beneficial for people with PDN. We measure only 4 out of 6 PF processes, not including values-based actions and present-moment awareness, because these facets sample from each of the broader categories of "openness," "awareness," and "engagement," dimensions of PF, and at the same time leave out the facets that we felt are least well assessed at the time the study was planned. Two "openness" facets were included: acceptance because it is the most studied and easiest to compare with other studies, and cognitive defusion because it was deemed important to include a cognitive component in the study due to the high importance placed on cognitive processes in all current psychological models of chronic pain. We predicted that each process measured here would be relevant and that a potentially important role would be shown significant correlations between measures of PF and measures of pain and daily functioning in this group, and significant increments of explained variance in multivariate analyses.

2. Methods

2.1 Study design and participants

The current study was a cross-sectional survey of adults with Type 1 and Type 2 diabetes and PDN. Participants were included regardless of any treatment they were receiving. The sample was recruited from pain and diabetes hospital services, from Diabetes UK (DUK), other websites designed to support people with pain, and via social media (i.e. Twitter). The recruitment started on 6 of February 2018 and finished on 6 of May 2018.

2.2 Sample size

A priori estimation was used to determine the required sample size based on several considerations. First, for multiple regression analyses, we based our estimate on similar studies (Billingham, Whitehead, & Julious, 2013; Chilcot et al., 2015). We also based it on modelling a regression

equation with 12 predictors and an effect size (Muller & Cohen, 1989) of f^2=0.15 (medium effect), with power set at 0.80. This suggested a need for a sample size of at least 127. Finally, we also considered possible missing data, and the need for an adequate sample size for secondary validity analyses of the instruments being used, as well as sensitivity analyses based on the mode of recruitment. We thus aimed to recruit a minimum of 200 participants.

2.3 Procedure

Ethical approval was gained for this study (Surrey Research Ethics Committee, 29/1/2018. Ref: 17/LO/2047). Informed consent was obtained from all participants, described below in more detail.

The inclusion criteria for this study were having an age of 18 years or more, living in the UK, having either a confirmed or self-reported diagnosis of diabetes mellitus (DM), having suffered from self-reported PDN for the last three months or more, having the ability to take part in the study, and the ability to provide informed consent. Diabetes diagnosis was assessed, using one participant self-report question. We also screened for possible neuropathic pain by one self-report question and the validated screening questionnaire, Douleur Neuropathique 4 (DN4). DN4 was not administered to the whole sample, but to a subgroup of participants, as it was not initially a high priority concern to obtain this kind of screening data, and in order to reduce the length of the survey. Also, the study did not have the resources to contact participant's general practitioners and diabetes specialists for further information for those recruited online. We assume that people would only self-identify as having PDN if they had actually been given that diagnosis, and any exceptions to this would be rare. Participants recruited from the hospital services also had a physician's diagnosis for DM and PDN.

Potential participants who were not able to understand verbal explanation or written information in English were excluded from the study, as no resources were available to translate the survey or to produce and validate the standardized measures being used in other languages.

Participants were recruited either online or face-to-face through hospital services. In particular, within the hospital services, participants were identified by diabetes and pain clinical care teams. A member from our research team (KK) then approached the potential participants, in the relevant outpatient clinics, explained the study and answered questions. Participants who agreed to take part then gave consent and received the recruitment pack.

A total of 120 participants were initially approached in person. Of the 120 invited this way, 60 did not meet the inclusion criteria (N=25 not being diagnosed with diabetes, N=35 suffering from neuropathy due to other causes than diabetes), and 38 declined to take part. Reasons for non-participation included, the length of the questionnaires (N=16), not being able to understand written information in English (N=10), and some eligible participants declined to give a reason (N=12). A total of 14 completed the pen-and-paper version of the presented survey. Two out of the 14 participants did not adequately complete the questionnaire and were excluded. In total 12 participants were recruited from hospital services.

Online recruitment was conducted through sending targeted online invitations to diabetes organisations with an online presence and through social media. An email was sent to the charity Diabetes UK (DUK), explaining the study and the inclusion criteria of participants and asking to publicise it through any available means, such as special interest forums and their website. Within the email, there was also a link to the online version of the survey. DUK posted the link on the recruitment page (https://www.diabetes.org.uk/research/take-part-in-research) and forum. Recruitment was also done via Twitter and two discussion forums sponsored by charity supported websites, 'Pain Support' (https://painsupport.co.uk/) and 'Pain Concern' (http://painconcern.org.uk/how-we-help/forum/). Particularly, 130 people were recruited from DUK's website, 40 from DUK's forums, 7 from Twitter, 17 from Pain Support forum and 19 from Pain Concern forum. In total 213 participants were recruited from online sites. This dual method of

recruitment, in clinic and online, aimed to include a wider sample of people suffering from PDN and achieving the targeted sample size.

2.4 Measures

The participants who agreed to take part in the survey completed a series of psychometrically validated assessment measures. The following additional variables were assessed through self-report questions: age, gender, ethnicity, education, work status, marital status, type of diabetes, presence of neuropathy, duration of pain, and specific pain locations. The survey was administered via paper or a widely available survey platform, Bristol Online Survey (BOS, https://www.onlinesurveys.ac.uk/). This is an easy to use portal to create a survey and used by many institutions. BOS is flexible and does not require any technical knowledge to set-up the survey or collect the data.

2.4.1 Chronic Pain Acceptance Questionnaire (CPAQ-8)

The CPAQ-8 is a measure of acceptance of chronic pain. It includes engagement in activities while experiencing pain and willingness to experience pain without trying to control or avoid it (McCracken et al., 2004; McCracken, & Velleman, 2010). CPAQ-8 is based on the 20-item questionnaire, and this version consists of 8 items and has also been fully validated (Fish, McGuire, Hogan, Morrison, & Stewart, 2010). Items are rated on a scale from 0 (never true) to 6 (always true). Higher scores reflect greater acceptance of pain. In the current sample, the CPAQ-8 demonstrated good internal consistency (Cronbach's α =0.87).

2.4.2 Cognitive Fusion Questionnaire (CFQ-7)

The CFQ-7 is a measure of cognitive fusion (Gillanders et al., 2014). Cognitive fusion refers to a domination of cognitive influence over direct experiential influence on behaviour, and a lack of separation between the content of the thoughts and the situations or people to which they refer.

Cognitive defusion, on the other hand, is the ability to see thoughts as just thoughts, and not as essential reflections of events as they are directly experienced. The CFQ-7 consists of seven items rated on a 1 (never true) to 7 (always true) point scale. An early version of the CFQ has been validated in chronic pain samples based on significant predicted correlations with acceptance and daily functioning in people with chronic pain (McCracken, DaSilva, Skillicorn, & Doherty, 2014). The updated version was used in the present survey. In the current sample, the CFQ-7 demonstrated good internal consistency (Cronbach's α =0.95).

2.4.3 Committed Action Questionnaire (CAQ-8)

The CAQ-8, is an eight-item measure of committed action, a facet of PF (McCracken, 2013; McCracken, Chilcot, & Norton, 2014). Committed action is the ability to persist with actions that are guided by goals, including when this runs into discouraging experiences and to change these actions when they are shown to be ineffective. Responses to the items were rated from 0 (never true) to 6 (always true). Out of the eight items four are positively keyed and four negatively keyed. Scores from the CAQ-8 have demonstrated relations with measures of acceptance, and of emotional, physical, and social functioning in people with chronic pain, supporting construct validity (McCracken et al., 2014). In the current sample, the CAQ-8 demonstrated good internal consistency (Cronbach's α =0.81).

2.4.4 Douleur Neuropathique 4 (DN4)

Presence of neuropathic pain was assessed with a screening measure called DN4. It consists of four interview questions and has also been psychometrically validated as a self-report measure (Bouhassira et al., 2005). It has a specificity of 83% and sensitivity of 90% (Spallone et al., 2012). In the current sample, the DN4 demonstrated adequate internal consistency (Cronbach's α = 0.75). This questionnaire was only administered to a subsample (N=75), to reduce the length and burden of the survey. The subsample was selected from their response to a question at the end of the survey

asking if they would be willing to take part in further research, if they answered 'yes', we contacted them and asked them to respond to the DN4. The purpose was to give evidence to support, or essentially validate, the self-report method which was used in the full sample.

2.4.5 Pain Scale

Pain intensity and pain-related distress were assessed through four validated questions using 0 (no pain/distress) to 10 (worst possible pain/distress) numerical ratings. Participants were asked to rate their pain right now and in the past week, and how distressing their pain is right now and in the past week (Jensen, Turner, Romano, & Fisher, 1999; Von Korff, Ormel, Keefe, & Dworkin, 1992). In the current sample the reliability of the pain intensity and pain distress scale was calculated with the Spearman-Brown formula, due to the fact that each scale has only two items and is was r= 0.86 in each case (Eisinga, Grotenhuis, & Pelzer, 2012).

2.4.6 Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a widely used, reliable and validated, measure used as an index for depression severity. It includes ten items based on DSM-IV. The first nine items reflect severity of depression symptoms and each is rated on a scale from 0 (not at all) to 4 (nearly every day). The last item, item ten, is a measure of impact of depression and is rated from 'not difficult at all' to 'extremely difficult' - this item was used as an additional variable to study here because within the psychological flexibility model the impact of symptoms of functioning is regarded as a particularly important potential outcome in treatment. The higher score for the sum of the nine items indicates higher levels of depression severity (Kroenke, Spitzer, & Williams, 2001). In the current sample, the PHQ-9 demonstrated good internal consistency (Cronbach's α =0.84).

2.4.7 Self Experiences Questionnaire (SEQ)

The SEQ is a 15-item self-report measure of self-as-context, within the PF model (Yu, McCracken, & Norton, 2016). This "contextual self" is defined as a sense of self that is not based upon self-evaluations and is separate from one's thoughts and feelings. This could also be referred as, taking a point of view on one's psychological experiences, seeing oneself as distinct from one's psychological experiences, or as "perspective taking". All items are rated on a scale from 0 (never true) to 6 (always true). All items are positively keyed, and higher scores indicate higher PF. The construct validity of the SEQ has been supported in demonstrated significant expected correlations with acceptance, committed action, and decentring, and with depression and daily functioning in people with chronic pain (Yu et al., 2016). In the current sample, the SEQ demonstrated good internal consistency (Cronbach's α =0.98).

2.4.8 Work and Social Adjustment Scale (WSAS)

The WSAS is a five-item, reliable and validated self-report measure of impairment in work and social functioning, or as we label here, "functional impairment" (Mundt, Marks, Shear, & Greist, 2002). WSAS items refer to work, home management, social and private leisure, and relationships. Each item is rated from 0 (no impairment) to 8 (very severe impairment). The validity of the WSAS is supported by significant correlations with measures of psychiatric symptoms and it is shown to be sensitive to the effects of treatment (Mundt et al., 2002). In the current sample, the WSAS demonstrated good internal consistency (Cronbach's α =0.93).

2.5 Statistical Analyses

The collected data were analysed with the Statistical Package for Social Science (version 18.0 IBM, SPSS). Limited missing data in the standardized inventories were substituted by mean imputation. The total sample size was 225 participants. Descriptive statistics, including means and standard

deviations (SDs) for continuous variables and frequencies and percentages for categorical variables, were calculated for the sample.

All standardized measures were scored according to their standard instructions. The variables consisting the PF facets were: acceptance of chronic pain (CPAQ-8), cognitive fusion (CFQ-7), committed action (CAQ-8), and self-as-context (SEQ). The dependent variables of the study were pain and pain-related distress (pain scale), functional impairment (WSAS), depression (PHQ-9), and depression impact (PHQ-9 item 10). Preliminary analyses included *t*-tests and correlation analyses examining relations between the pain outcomes and functioning variables and the PF variables with individual's background characteristics.

Three sets of analyses were conducted to address the main purpose of this study. The first set included correlation analyses between the four PF variables, with pain, functional impairment, and depression variables. These analyses were conducted to first identify significant unadjusted relationships between these variables in order to then proceed to a multivariate approach with linear, hierarchical, multiple regressions. Multiple regression analyses were designed both to consider and statistically control the role of age, education, sex, pain duration, and pain intensity, and to examine the proportion of variance accounted by acceptance of chronic pain, cognitive fusion, committed action, and self-as-context, uniquely and combined, in relation to the measures of participant's functioning.

3. Results

3.1 Sample Characteristics

A total of 225 people participated in this survey. The mean age of all participants was 52.05 (SD= 12.06) years. Women represented 64.9% of the sample and white ethnicity 82.2%. The mean years of education was 14.98 (SD=3.76) and mean years of pain duration was 7.16 (SD=9.02). Employment status was categorized as follows: full-time employment (24%), employed part-time due to pain

(22%), employed part-time due to other reasons (13%), retired (24%), unemployed due to pain (10%), and full-time student (7%). The mean DN4 score was 7.15 (SD =2.39) and 92.7% exceeded the cut-off, an overall score of 4, for neuropathic pain. The 12 participants recruited from hospital services and 213 from online did not differ on background variables or the measures of psychological flexibility or pain outcome measures and were treated as one sample.

3.2 Preliminary analysis

Each primary variable was examined for normality by using histograms, Q-Q plots, and indices of skewness and kurtosis. None of the primary measures in this study produced significantly skewed distributions or outliers expected to adversely affect correlation-based analyses. The total scores of all measures were considered normally distributed. See Table 13 for means, ranges and standard deviations for the primary study variables.

Pain intensity and distress variables differed significantly by gender, with men reporting higher scores of pain intensity, $t = -3.09$, $p < 0.01$, and pain-related distress, $t = -2.86$, $p < 0.01$. Participants of white ethnicity reported lower scores in terms of committed action, $t = -2.64$, $p < 0.01$, functional impairment, $t = -2.96$, $p <0.01$, and self-as-context, $t = -3.82$, $p < 0.01$, than the non-white group of participants. Employed participants scored significantly lower in terms of committed action, $t = -2.73$, $p < 0.01$, functional impairment, $t = -2.97$, $p <0.01$, and self-as-context, $t = -3.44$, $p < 0.01$ variables than those who are not employed.

Preliminary correlation analysis showed that age was correlated with committed action, depression severity, and self-as-context, $r = -0.23$, $p < 0.01$; $r = 0.19$, $p < 0.01$, and $r = -0. 24$, $p < 0.01$ respectively. Years of education was found to be correlated with all primary variables except cognitive fusion, including pain intensity: $r = 0.20$, $p < 0.01$; acceptance of pain: $r = -0.16$, $p < 0.05$; committed action: $r = -0.20$, $p < 0.01$; depression severity: $r = 0.21$, $p < 0.05$; functional impairment: r

= 0.21, $p < 0.01$; self-as-context: $r = -0.14$, $p < 0.05$. Duration of pain was not significantly correlated with any of the variables.

Table 13: Means and standard deviations for standardized psychological flexibility variables, health and functionality outcome variables (N = 225)

	Possible Range	Sample Mean	Standard Deviation
Pain intensity (Rating Scales)	0-10	4.31	2.24
Pain distress (Rating Scales)	0-10	4.52	2.43
Functional impairment (WSAS)	0-40	17.67	11.48
Depression severity (PHQ-9 items 1-9)	0-27	12.05	7.00
Depression impact (PHQ-9 item 10)	0-3	1.83	0.64
Acceptance of pain (CPAQ-8)	0-48	25.01	4.88
Cognitive fusion (CFQ)	7-49	24.33	11.06
Committed action (CAQ-8)	0-48	21.08	8.16
Self-as-context (SEQ)	0-90	40.98	21.17

3.3 Correlation analyses

The four primary PF variables were not found to be correlated with each another at a level that would suggest problems of multicollinearity in regression analyses ($r < .80$, Grewal, Cote, & Baumgartner, 2004). In fact, the highest correlation between these variables was r =.54. Please see Table 14.

Correlations between acceptance of pain, cognitive fusion, self-as-context, and committed action and pain intensity with pain-related distress, functional impairment, depression severity, and depression impact are included in Table 15. Pain intensity positively correlated with pain distress, $r=0.87$, $p<0.01$, functional impairment, $r=0.57$, $p<0.01$, depression severity, $r=0.51$, $p<0.01$, and

depression impact, r=0.40, p<0.01. Acceptance of pain negatively correlated with pain intensity r=-0.21, p<0.01, pain distress, r=-0.25, p<0.01, functional impairment, r=-0.38, p<0.01, depression severity, r=-0.41, p<0.01, and depression impact, r=-0.41, p<0.01. Cognitive fusion positively correlated with pain intensity r=0.14, p<0.05, functional impairment, r=0.24, p<0.01, depression severity, r=0.44, p<0.01, and depression impact, r=0.20, p<0.01. Additionally, committed action negatively correlated with functional impairment, r=-0.22, p<0.01, depression severity, r=-0.43, p<0.01, and depression impact, r=-0.21, p<0.01. Lastly, self-as-context negatively correlated only with depression severity, r=-0.31, p<0.01.

Table 14: Primary correlation analysis among psychological flexibility variables (N=225)

	1	2	3	4
1. Acceptance of pain	-			
2. Cognitive fusion	-.25*			
3. Committed action	.40**	-.42**		
4. Self-as-context	.27**	-.20**	.54**	-

* p < .05, two-tailed

** p < .01 two-tailed

Table 15: Correlations between psychological flexibility variables, health and functioning, and pain

	Pain intensity	Pain distress	Functional impairment	Depression severity	Depression impact
Pain intensity	-	.87**	.57**	.51**	.40**
Acceptance of pain	-.21**	-.25**	-.38**	-.41**	-.41**
Cognitive fusion	.14*	.12	.24**	.44**	.20**
Committed action	-.05	-.12	-.22**	-.43**	-.21**
Self-as-context	-.05	-.07	-.07	-.31**	.00

* $p < .05$, two-tailed

** $p < .01$ two-tailed

3.4 Multiple regression analyses

Multiple regression analyses were conducted to examine the unique and combined role of PF variables, after adjusting for individuals' characteristics and pain intensity, in relation to the measures of health and functioning: pain-distress, functional impairment, depression severity, and depression impact. Hence four regression equations were conducted.

The potential predictors were tested hierarchically in each of these equations. Participants' age, gender, education and duration of pain were firstly tested and retained in the equations when significant (first block, $p < 0.05$ to enter, $p > 0.10$ to remove). Afterwards, the pain intensity average score was entered to control its contribution to the prediction of each criterion variable (second block). Finally, acceptance of pain, cognitive fusion, committed action, and self-as-context scores were entered together in a single block to examine their contribution. The regression results are shown in Table 16.

Education was entered and retained as a significant predictor at entry into all the equations. However, the regression coefficient for education did not remain significant in the final step of all

the regression equations. It should be noted that education accounted for modest increments of variance at entry, no more than 7.7%. Gender and duration of pain were not significant predictors at entry in the equation for depression impact, depression severity or functional impairment. Gender was a significant predictor of pain distress, with men experiencing more pain distress than women, explaining 3.1% of the variance. Gender did not remain significant in the final step of the regression equation. Finally, age was a significant predictor of both depression impact and depression severity and accounted for a 3.0% and a 2.3% increment of variance, respectively. As age increased, depression impact and depression severity also increased. Age remained significant only in the final step of depression impact regression equation.

The pain intensity variable was a significant predictor at entry and remained significant in all the equations. In the equation for functional impairment, pain intensity had the largest regression coefficient and the ΔR^2 (change in variance or R^2) value, higher than that of the four PF variables combined, reflected 32.2% of the variance. In the equation for depression severity, pain intensity once again had the largest regression coefficient and the ΔR^2 value, close to that of the four PF variables combined, reflected 23.3% of the variance. In the equation for pain distress, pain intensity had the largest regression coefficient and the ΔR^2 value, higher than that the four PF variables combined, reflecting 67.1% of the variance. In the equation for depression impact, pain intensity had the largest regression coefficient and the ΔR^2 value, close to that of the four PF variables combined, reflected 13.2% of the variance.

The combination of the four variables representing PF variables accounted for a significant increment of variance in all the equations except in the case of pain distress. In the equation for functional impairment, PF variables accounted for 4.5% of the variance, although only the coefficient for acceptance of pain was significant. In the case of depression severity, acceptance of pain, cognitive fusion and committed action had significant regression coefficients and the variance accounted for was 7.5%. In the case of pain distress, no significant regression coefficient was found

from among the PF variables. In the case of depression impact, acceptance of pain and self-as-context had significant regression coefficients and the variance accounted for was 11.4%.

Standardized regression coefficients and the squared semi-partial correlation coefficients reveal the relative role of the four separate processes when considered together. Mean proportions of unique variance contributed (sr^2) from all the equations were as follows: acceptance of pain, 0.033, cognitive fusion, 0.011, committed action, 0.008, pain intensity, 0.294, and self-as-context, 0.011.

Table 16: Multiple regression analyses of psychological flexibility variables with measures of health and functioning

Block	Predictor	Beta (final)	ΔR^2 (block)	sr^2	Adjusted total R^2
Pain distress					
1	Duration of education	.100**	.061**	.009	
2	Gender	-.015	.031*	.000	
3	Pain intensity	.851**	.671**	.642	
4	Acceptance of pain	-.012	.003	.000	
	Cognitive fusion	-.027		.001	
	Committed action	-.072		.003	
	Self-as-context	.034		.001	.757**
Functional impairment					
1	Duration of education	.081	.045**	.006	
2	Pain intensity	.532**	.322**	.264	
3	Acceptance of pain	-.218**	.068**	.037	
	Cognitive fusion	.062		.003	
	Committed action	-.075		.003	
	Self-as-context	.053		.002	.417**
Depression severity					
1	Duration of education	.061	.042**	.003	
2	Age	.079	.030*	.006	
3	Pain intensity	.436**	.233**	.178	
4	Acceptance of pain	-.158**	.187**	.019	
	Cognitive fusion	.228**		.041	
	Committed action	-.165*		.015	
	Self-as-context	-.064		.003	.473**
Depression impact					
1	Duration of education	.173**	.077**	.027	
2	Age	.131*	.023*	.015	
3	Pain intensity	.314**	.132**	.092	
4	Acceptance of pain	-.313**	.126**	.075	
	Cognitive fusion	.000		.000	
	Committed action	-.136		.010	
	Self-as-context	.237**		.039	.334**

* p < .05, two-tailed, ** p < .01, two-tailed

4. Discussion

PDN is a complex condition and one of the most distressing complications of DM (Galer et al., 2000; Selvarajah et al., 2014). Despite this, existing studies of psychological variables mainly focus on pain intensity as an outcome in relation to depression and anxiety without exploring the other potentially therapeutic psychological processes. For the first time in a study of PDN, facets of PF were carefully assessed, using validated questionnaires, and examined in relation to standard measures of pain and functioning.

This study demonstrated significant correlations between PF variables and functional impairment, depression severity, and depression impact in people with PDN. These results are consistent with the results of previous studies that support the role of PF in people with general, usually musculoskeletal, pain, including studies particularly focused on acceptance of pain (Mason et al., 2008; McCracken, 1998; Nicholas & Asghari, 2006; Viane et al., 2003), cognitive defusion (McCracken et al., 2014), mindfulness (McCracken, MacKichan, & Eccleston, 2007) and value-based action (McCracken et al., 2007), and committed action (McCracken, 2013).

In this study, we found mostly small correlations between PF and the dependent variables, functional impairment, depression severity, and depression impact, and relatively larger correlations between pain and some of these same variables, particularly so for functional impairment, less for the depression variables. While PF appears as a plausible contributor, pain severity generally appears to play a more important role in relation to daily functioning in PDN. This result is different in this sense from studies of other populations where the role of PF facets in daily functioning and wellbeing appears greater and the role of pain itself appears smaller, including studies of mixed pain conditions (McCracken & Velleman, 2010; McCracken & Zhao-O'Brien, 2010), low back pain (Mason et al., 2008), fibromyalgia (Wicksell et al., 2012; Yu et al., 2017) and headache (Almarzooqi, Chilcot, & McCracken, 2017; Foote, Hamer, Roland, Landy, & Smitherman, 2015). Taking into account that the role of PF is smaller than expected, this could be due to as yet unidentified differences in the

experience of neuropathic pain. There are so few psychological studies in neuropathic pain, however, it is too soon to confirm the current results or propose an explanation.

Studies investigating outcomes following treatment have demonstrated a moderate-sized negative relationship between changes in PF variables and pain interference (Wicksell, Ahlqvist, Bring, Melin, & Olsson, 2008) and pain-related anxiety, depressive symptoms, physical and psychosocial disability (McCracken & Gutiérrez-Martínez, 2011; McCracken & Jones, 2012; Vowles, McCracken, & O'Brien, 2011). These results suggest that if PF is increased this would lead to the improvements in a wide range of outcomes. It remains to be seen if this would happen in PDN.

Regression analyses here show that PF variables may play a significant role in functional impairment, depression severity and depression impact, even when other relevant factors are considered, including background variables and pain intensity. Acceptance of pain appeared to contribute the greatest proportion of variance among the PF variables. In general, this suggests that these variables may afford a route toward improved functioning that is independent of pain severity in this population.

It may be worth mentioning that compared to previous pain research our sample was older (by approximately 10 years) (i.e. McCracken & Velleman, 2010), but it was consistent with PDN research (i.e. Geelen et al., 2017). This might suggest that the added challenges that can come with ageing (i.e. co-morbid conditions, polypharmacy, cognitive impairment) need to be better addressed within an ACT based programme for older people (Scott et al., 2017). Participants in the current study were more likely to be employed either part-time or full-time, and they reported a lower level of acceptance of pain than other studies. The sample recruited from hospital services and online did not appear to differ. It remains the case, however, that the applicability of the current results to specific subpopulations with PDN will need to be further examined.

As far as we are aware, only four studies of psychological treatments have been conducted including individuals with PDN, most of them were either small in scale or produced limited results (Otis et al., 2013; Nathan et al., 2017; Pfammatter, 2010; Teixeira, 2010). Clearly more research needs to be done, including into the structure and mode of delivery and into the choice of treatment methods. It appears reasonable, based on present findings, to next incorporate the components of PF into a pilot or feasibility trial.

ACT has been applied successfully to individuals with chronic pain and has growing support (Hann & McCracken, 2014; McCracken & Morley, 2014; Veehof et al., 2016). We know that online treatment in particular, is increasingly used. A brief online treatment for chronic pain in general, based on ACT, has been demonstrated feasible within a mixed specialty pain treatment population in the UK (Scott et al., 2018b). This type of delivery format and similar content could provide efficient means for further treatment development for PDN.

This study addresses new questions and produces new findings. At the same time, it has a number of limitations. Because of the cross-sectional design and reliance on self-report measures, it can include biases. Self-reports may include some participants not reporting their actual behaviour and views, which may compromise the accuracy of the results. Also, it did not include either analysis of variables over time or an experimental manipulation. No conclusions about causal relations between PF and functioning are possible. Furthermore, the questionnaire was also accessed online anonymously. This means diagnoses could not be verified. This also makes it possible for participants to access it more than once, although the length of the questionnaire certainly would discourage participants from doing this. Also, recruitment among those seeking treatment in the hospital services was limited (10%). It is possible that results may have been different if that type of recruitment had been more successful. Lastly, our results cannot be automatically generalised to any specific groups within the larger population of people with PDN, groups characterised by specific

ethnicity, age, comorbidities, and other factors. If the sample had been different in any of these ways, the results could have been different.

In conclusion, based on the collected data of this cross-sectional observational study, facets of PF are associated with pain, emotional experiences, and difficulties experienced in daily life activities of individuals with PDN. Meanwhile, the unexpected relatively larger role that pain intensity appears to play in the PDN population calls for replication. If a significant role for pain itself is confirmed as reliable, perhaps we need to search more vigorously for effective remedies for pain itself. Further study of psychological factors in general in the context of PDN is encouraged to support the design and evaluation of psychological treatments for individuals suffering from PDN, a condition that has been the subject of very few psychological treatment studies. A psychological treatment focusing on psychological flexibility, rather than on symptom control, may represent an important new option, an addition to the current almost complete reliance on analgesic medication only.

4.3 Summary

This was a cross-sectional survey of PF facets in adults with PDN. Key results suggested that compared to previous chronic pain studies, PF seems to play a smaller role in the daily functioning of people with PDN while pain intensity is a stronger contributor. At the same time the correlations observed appear statistically significant in most of the instances tested, and the size of the relations, mostly small on average, are similar to the size achieved by measures of variables included in previous generations of psychological treatments, particularly measures of coping and beliefs (Jensen & Turk, 2014).

4.4 Rationale for Proceeding with the Online ACT Treatment

The cross-sectional survey demonstrated that pain intensity (accounting for 32.2% of the variance) plays a more important role than PF (accounting for 6.8% of the variance) in people with PDN. However, it was decided to proceed with the online ACT treatment for people with PDN targeting PF for the following reasons:

- Pharmacological interventions target pain reduction (Griebeler et al., 2014), and therefore pain intensity, while psychological treatments target other aspects, such as behaviour change, to improve coping with pain. Therefore, PF is still potentially relevant to this population.
- This study demonstrated that face to face recruitment from NHS clinics was less successful than from online advertisements. An explanation for this is that it is difficult to identify people with PDN attending diabetes clinics due to the lack of adequate coding of PDN diagnosis. Therefore, given online recruitment was successful an online treatment was deemed appropriate.
- The online ACT treatment that was available, through the platform ACT4PAIN, has been successfully delivered to people with general chronic pain (Scott et al., 2018b). The results suggested small effects for decentring, functioning, medication, committed action and healthcare use, medium for mood and large for acceptance.

Chapter 5: Feasibility Single-Cohort Study of Online Acceptance and Commitment Therapy for People with Painful Diabetic Neuropathy in the United Kingdom

5.1 Chapter Overview

The study in this chapter was underpinned by the theory and philosophy of the PF model and ACT, the available data to support the efficacy of ACT, and the findings from the earlier described systematic review and cross-sectional survey. The systematic review identified the lack of research into psychological interventions for the treatment of pain for people with PDN compared to the general chronic pain population. This chapter examines the feasibility of an online version of ACT-based treatment for the PDN population in the UK and investigates whether a larger RCT is justified. The design and content of the ACT treatment will be described in detail and the main treatment materials, including experiential exercises and metaphors, and programme schedule are presented.

This chapter is published in the following article at Pain Medicine journal (Appendix Q):

Kioskli, K., Scott, W., Winkley, K., Godfrey, E., & McCracken, L. M. (2019). Online Acceptance and Commitment Therapy for people with painful diabetic neuropathy in the United Kingdom: A single-arm feasibility trial. *Pain Medicine (Accepted/In Press).*

Chapter naming and numbering are presented as they are in the published article.

5.2 Published Article

Manuscript Number: PME-ORR-Sep-19-797

Title: Online Acceptance and Commitment Therapy for people with painful diabetic neuropathy in the United Kingdom: A single-arm feasibility trial

Article Type: Research Article

Corresponding Author: Lance M McCracken, PhD

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Conflicts of interest: None declared.

Note: This is the author's accepted copy.

Abstract

Objective: This study aimed to assess the feasibility of online ACT for PDN in the United Kingdom and to determine if a larger randomised controlled trial testing treatment efficacy is justified.

Methods: Participants with PDN were recruited online and from hospital services. This was a single-arm study in which all participants received online ACT. Participants completed questionnaires at baseline and 3-month post-treatment. Primary feasibility outcomes were recruitment, retention, and treatment completion rates. Secondary outcomes were pre- to post-treatment effects on pain outcomes and psychological flexibility (PF).

Results: From 225 potentially eligible participants, 30 took part in this study. Regarding primary feasibility outcomes, the treatment completion and follow-up questionnaire completion rates were 40% and 100%, respectively. Generally, at baseline those who completed the treatment, compared to those who did not, had better daily functioning and higher PF. With respect to secondary outcomes, results from the completers group showed clinically meaningful effects at post treatment for 100% of participants in pain intensity and pain distress, 66.7% in depressive symptoms, 58.3% in functional impairment, 41.7% in cognitive fusion, 66.7% in committed action, 58.3% in self-as-context, and 41.7% in pain acceptance.

Conclusions: This preliminary study suggests feasibility of recruitment and follow-up questionnaire completion rates supporting planning for a larger randomised control trial. However, treatment completion rates did not achieve the pre-specified feasibility target. Changes to the treatment content and delivery may enhance feasibility of ACT for people with PDN on a larger scale, however this needs further investigation.

Keywords: painful diabetic neuropathy, acceptance and commitment therapy, feasibility study

1. Introduction

PDN is a complex pain condition and a known complication of diabetes with a prevalence of 25-30% (Daousi et al., 2004; Geelen et al., 2017). The main symptoms are tingling and burning sensations in hands and feet that can have a significant impact on daily functioning (Geelen et al., 2017; Kioskli et al., 2019). Psychosocial factors, such as depression, anxiety and sleep are significantly associated with PDN (Kioskli et al., 2019). At the same time current treatment options are mainly pharmacological, which appear to produce limited benefits (Finnerup et al., 2016). The experience of pain, and how pain is viewed by others, may differ in this population compared to other populations suffering from chronic pain of mainly musculoskeletal origin (Coghill, 2010; Kioskli et al., 2019).

ACT is a newer, contextual form of CBT that incorporates acceptance, mindfulness, and values-based behaviour change (Hayes et al., 1999). It specifically focuses on increasing psychological flexibility (PF) (Hayes et a., 2011), which includes six processes: acceptance, cognitive defusion, awareness of the present moment, self-as-context, committed action, and values-based actions (Hayes et al., 2006).

Systematic reviews show that CBT is effective for chronic pain in general (Williams et al., 2012). ACT has a growing evidence base for the treatment of chronic pain and appears to produce outcomes similar to traditional CBT (McCracken & Vowles, 2014; Veehof et al., 2016). Furthermore, ACT may produce better results post-treatment regarding pain-related disability in comparison to alternative treatments, such as relaxation (Kemani et al., 2015).

ACT has not previously been evaluated in PDN (Kioskli et al., 2019). It is designed to be broadly applicable to different types of psychological and physical problems and may be particularly suited to multi-problem cases. Therefore, ACT may be a good fit to address the multiple impacts of pain and the range of physical and psychosocial comorbidities that people with PDN can experience (Dindo, Van Liew, & Arch, 2017; Kioskli et al., 2019). Additionally, ACT assumes that targeting a core

set of behavioural processes (i.e. PF) can lead to improved functioning and quality of life generally across these different problem areas. Thus, ACT for chronic pain may also help people with PDN without requiring specific adaptations.

A current challenge is that access to CBT and ACT for pain management is limited outside of specialist centres (Scott et al., 2018b). However, online treatments may address this, and they may be cost-effective, time-efficient, more acceptable, and less stigmatizing, than face-to-face treatments (Andersson, Cuijpers, Carlbring, Riper, & Hedman, 2014; Eccleston et al., 2014). Several studies have investigated online CBT and ACT for chronic pain, all yielding moderate to large improvements in pain and disability compared to waitlist controls or other psychological treatments (Andersson et al., 2014; Buhrman et al., 2013; Eccleston et al., 2014; Scott et al., 2018b; Trompetter, Bohlmeijer, Veehof, & Schreurs, 2014; Yang, Moss-Morris, & McCracken, 2017).

No studies have examined online ACT for PDN, despite the clear need, potential to enhance access and potential for cost-effectiveness. Therefore, the current study aimed to test the feasibility of online ACT for people with PDN, within the context of a single-arm study to identify if a larger RCT is possible and justified. The feasibility questions were whether online ACT would be acceptable to the PDN population, as reflected by adequate recruitment, follow-up questionnaire completion, and treatment completion rates. For each of these questions *a priori* criteria were set against which to determine feasibility. In terms of secondary feasibility questions, effect sizes were calculated to determine whether participants who received ACT treatment improved in terms of on pain outcomes and PF.

2. Methods

2.1 Study design

This study was an online single-arm (non-randomised) feasibility study. The treatment being tested was originally designed for individuals with chronic pain in general. NHS ethical approval was obtained from Surrey Research Ethics Committee (29/1/2018, Ref: 17/LO/2047). All participants gave informed consent and the protocol was registered at https://www.clinicaltrials.gov (NCT03700528). The study followed the ethical standards of the Declaration of Helsinki (1964) and its later amendments.

Participants completed assessment at baseline and 3-month follow-up through a secure survey platform (Bristol Online Survey; BOS). Even though the literature recommends RCT designs (Eccleston et al., 2014), the National Institute for Health Research highlights that not all feasibility trials should be randomised. The study's focus was on recruitment, retention for follow-up questionnaires, and treatment completion rates, which are aims that do not necessarily require randomisation.

The total sample size was calculated to allow reliable estimation of retention and completion rates, assuming a retention rate of 80%. The estimated sample size would allow for estimation of the true population consent rate with an 11% margin of error (95% CI) for eligible participants. Past research in chronic pain, conducted by the team, suggests consent rates between 50-70%, assuming a more conservative uptake of 40%, and that approximately 30% will meet the eligibility criteria. Additionally, a sample of 30 participants is in line with recommendations for feasibility study (Billingham et al., 2013).

2.2 Recruitment and Participants

The case definition was adults with PDN. The main inclusion criteria were (1) ≥18 years old; (2) diabetes and PDN diagnosis, which were identified through self-report questions, the Douleur Neuropathique 4 interview (DN4i), and a physician's diagnosis, when available; (3) verbal and written proficiency in English; and (4) computer literacy. Potential participants were excluded if their primary pain was not PDN. Please see Figure 14 for recruitment details. The 225 participants, initially approached, were participants from a previously conducted survey by the same authors (Kioskli et al., 2019). However, wider efforts for recruitment took place to reach the initial target. More specifically, participants were recruited via Guy's and St Thomas NHS Foundation Trust and online advertisements. Online invitations were sent and resulted in recruitment as follows: 'Diabetes UK' (https://www.diabetes.org.uk/research/take-part-in-research) (n=15), 'Pain Support' forum (https://painsupport.co.uk/) (n=8), 'Pain Concern' forum (http://painconcern.org.uk/how-we-help/forum/) (n=4) and Twitter (n=1). Final post-treatment questionnaires were collected in April 2019.

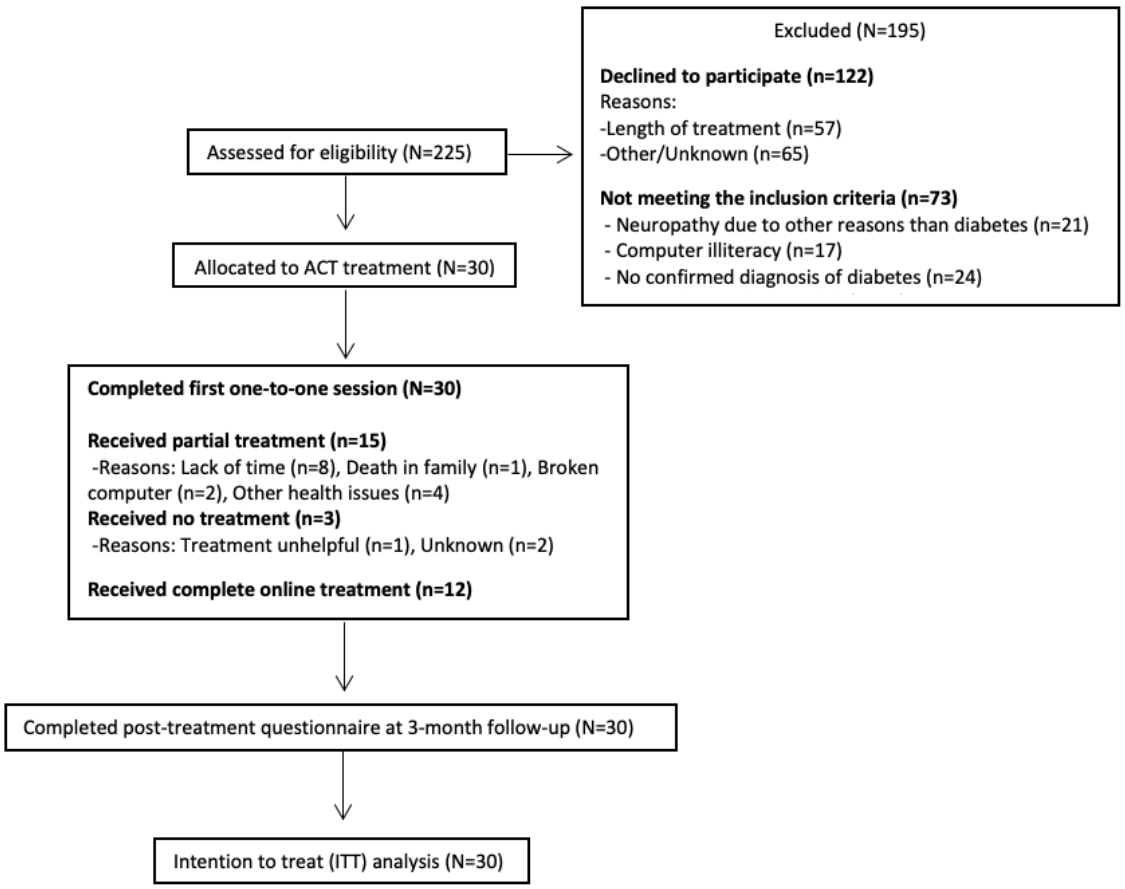

Figure 14: Study Flow Diagram

2.3 ACT Online Treatment

The purpose of this online therapist-supported treatment was to increase participants' PF - namely, their willingness to experience pain, awareness of experiences in the present moment, and engagement in committed and values-based actions (McCracken & Vowles, 2014). ACT was considered appropriate for this study, since PF is a transdiagnostic model and can be applied to various conditions with no need for any alterations (Dindo et al., 2017). ACT is theoretically well suited to a range of problem areas and, on average, people with a range of conditions benefit.

Online treatment procedures and content were based on the online version of ACT developed and initially tested by Scott et al. (2018b). The treatment involved one 30-45-minute Skype session with the therapist, at the beginning of treatment, to explain the treatment processes and set therapeutic

goals. The online treatment platform which was used was called ACT4PAIN (https://www.act4painonline.co.uk/#/), initially created by LM and WS. In the current study, the first author (KK) acted as the therapist. The therapist's experience level was Master's-level in health psychology, 6 months certified training on third wave CBT from the British Psychological Society (BPS), and further training from LMM and WS who are registered clinical psychologists, with experience providing ACT for chronic pain. WS provided ongoing supervision to discuss participants' engagement and challenging responses as they arose. Since KK acted as the therapist and analysed the collected data, direct data entry from each participant and remote/online assessment were used to reduce the influence of the researcher on the assessment.

Following the first Skype session, eight online sessions were provided in a 5-week period. This standardized package was delivered, two times per week, for the first 3 weeks, and one time per week for the final two weeks. The delivery was conducted according to the originally developed treatment by Scott et al. (2018b). Twice weekly sessions were chosen earlier in the treatment to keep participants focused on the treatment and practicing new skills. This was based loosely on a previously designed treatment (McCracken, Sato, & Taylor, 2013). Frequency of treatment sessions tapered off in final two weeks to foster greater independence in preparation for self-management after treatment completion. The sessions consisted of video and audio recordings that guided participants through experiential exercises, mindfulness practice, metaphors, values clarification and values-based goal setting (see examples in Figures 15 and 16). Online sessions included video and audio content that was between 12 and 35 minutes in duration (see Tables 17 and 18 for more details on treatment content). The total approximate time for the content delivered from the system was approximately 150 minutes.

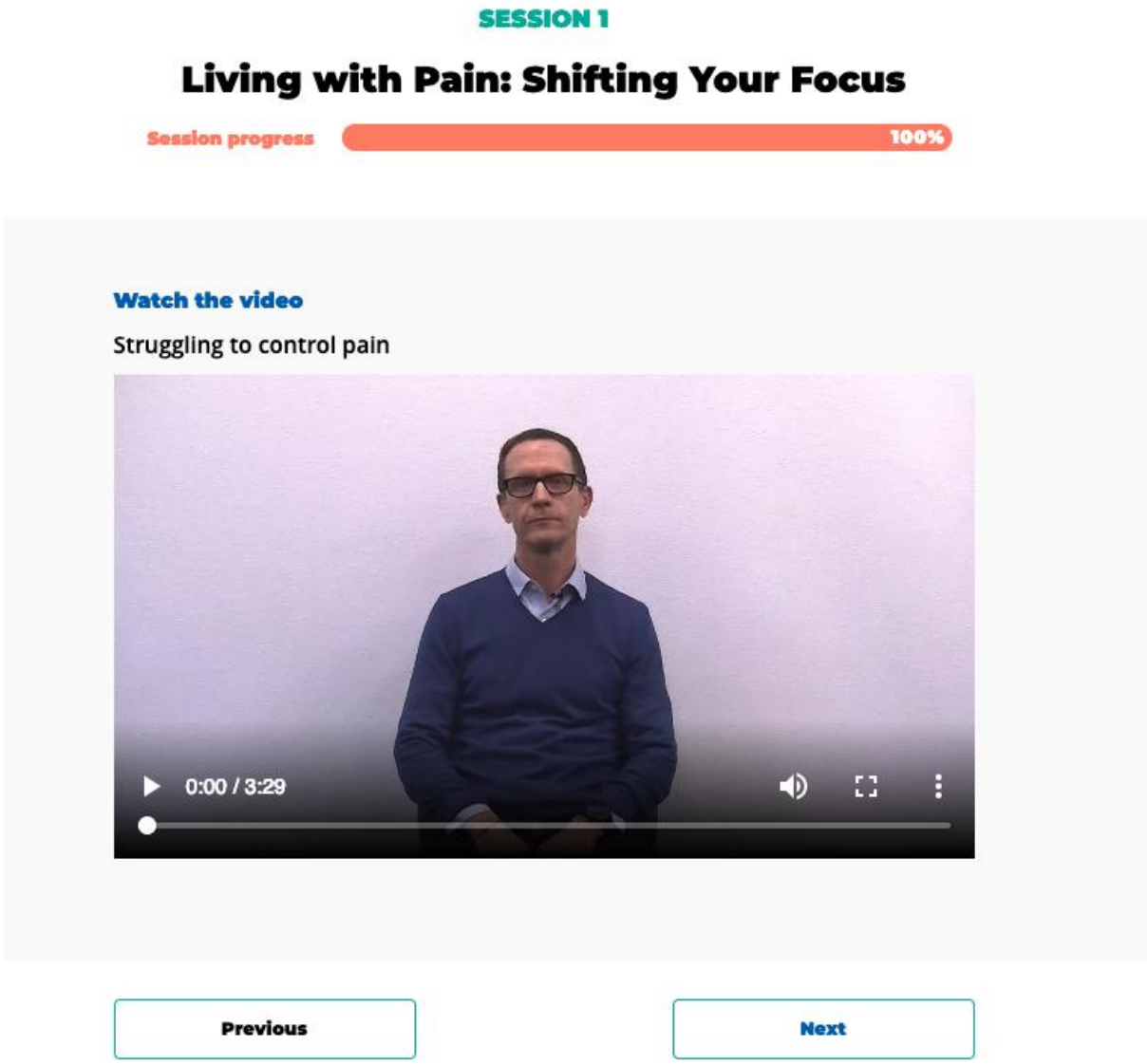

Figure 15: Example of video recording as shown in ACT4PAIN platform

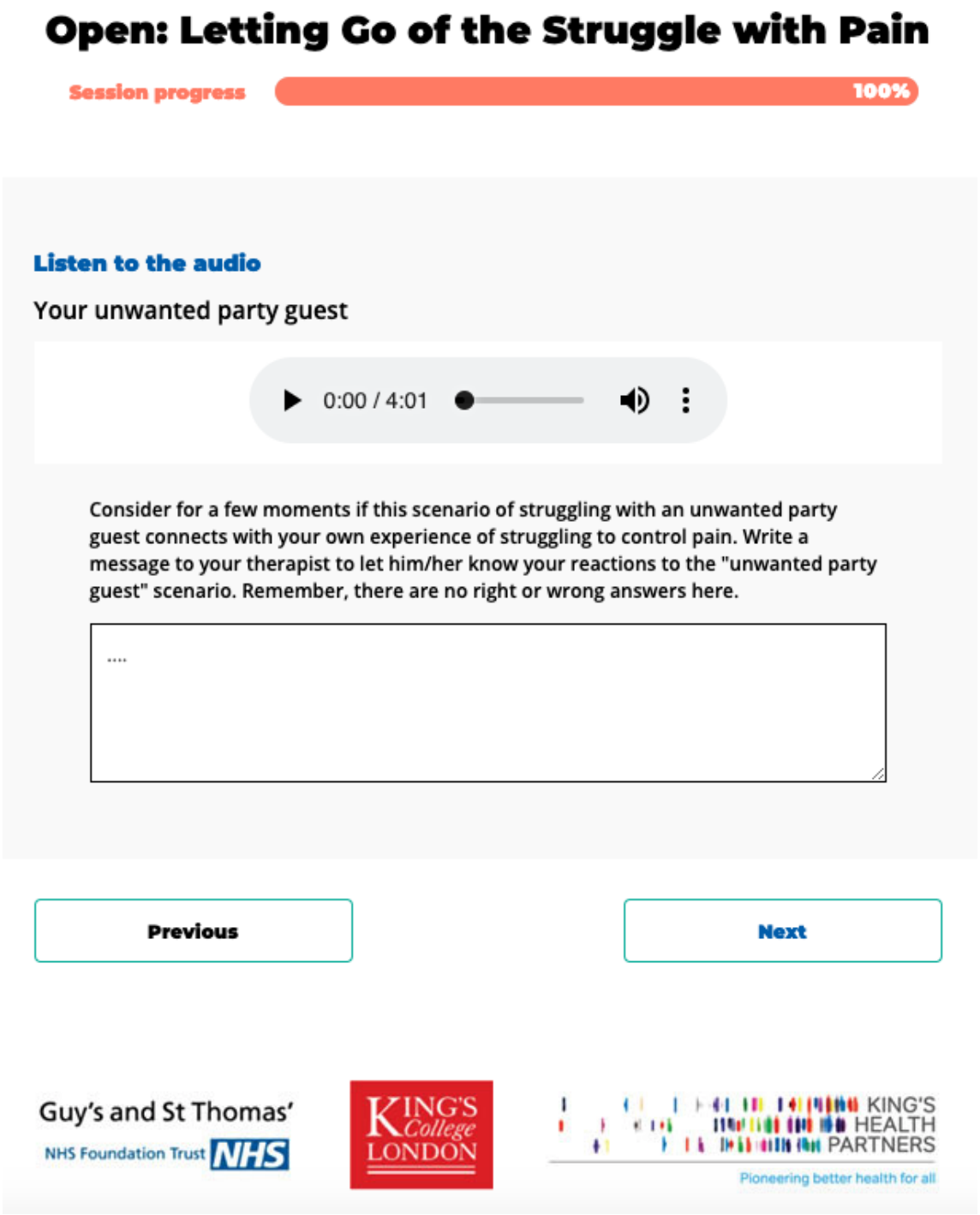

Figure 16: Example of audio recording as shown in ACT4PAIN platform

Table 17: Summary of ACT psychological treatment sessions

Sessions	Information	Tasks/Exercises	Total Video Running Time (Minutes)	Total Audio Running Time (Minutes)
Session **1**: Skype one-to-one	Introducing the treatment	Goal setting & Identify barriers	-	-
Session **2**: Online	Living with pain: Shifting your focus	Passengers on the bus metaphor & Notice 5 things exercise	6.16	10.86
Session **3**: Online	Open: Letting go of the struggle with pain	Unwanted party guest & Connect, breathe, open up exercise	3.99	12.16
Session **4**: Online	Open: Responding differently to thoughts	Mind experiments & Labelling thoughts exercise	7.01	17.63
Session **5**: Online	Engaged: Choosing your values and goals	Choosing your focus & 80th Birthday exercises & Values assessment form	6.32	10.52
Session **6**: Online	Aware: Focusing on the present moment	Tracking thoughts in time	7.23	27.08
Session **7**: Online	Engaged: Committing to your goals	The swamp metaphor, Small steps exercises & goal setting form	3.84	8.06
Session **8**: Online	Aware: A different point of view	'Observer self' exercise	4.94	17.32
Session **9**: Online	Building wider patterns of success	'Brief observer self-exercise', Your kind friend exercise, & goal setting form	4.16	10.87
Session **10**: Skype one-to-one	Committed action & Debriefing	Goal setting & Evaluation	-	-

Note: This format is based on the treatment in Scott et al.'s (2018b) trial.

Table 18: Overview of study procedures and treatment schedule

Week (0)	Week (1)	Week (2)	Week (3)	Week (4)	Week (5)	Week (6)	Week (7)	Week (12)
Participants give informed consent and respond to the baseline questionnaire	Skype session with the therapist, to help the navigation within the platform, set goals, identify barriers and answer any questions	Completion of sessions 2 and 3	Completion of sessions 4 and 5, based upon completion of the previous ones	Completion of sessions 6 and 7, based upon completion of the previous ones	Completion of session 8, based upon completion of the previous ones	Completion of session 9, based upon completion of the previous ones	Skype session to set future goals and evaluate the treatment	Participants receive an e-mail linked to a post-treatment questionnaire
Arrange the first Skype session	Participants gain access to the online program (username, password, hyperlink)	Participants access the next sessions if they completed these ones	Direct messaging with the therapist	Direct messaging with the therapist	Direct messaging with the therapist	Direct messaging with the therapist	-	-
-	-	Direct messaging with the therapist	-	-	-	Arrange the final Skype session	-	-

Note: Rows follow the order of actions undertaken per week.

At the start of each session participants provided ratings of their developing skills in the categories of openness, awareness, and engagement, on a scale from 0 (never) to 6 (always) in reference to the past three days (see Figure 17). These ratings were seen by the therapist who could then use the information to tailor feedback. During each session, participants were asked about their experience with the material and received individual written feedback from the therapist within 24 hours through secure in-site messaging. The feedback was meant to be individualized, to incorporate any particular challenges specific to PDN, and aimed to encourage engagement and to enhance PF. Participants received weekly reminders to complete sessions through messages generated by the website. When a participant expressed that they wished to drop-out, the therapist would ask the reason for discontinuation via in-site messaging, and whether the participant had any suggested refinements for the treatment which would encourage them to complete all the sessions When sessions were completed the therapist could see this, however, data on how frequently/for how long participants practiced the exercises between sessions were not collected. Collecting practice time information would be useful in a larger trial. However, therapist messages served to prompt practice and discuss any barriers or challenges around practicing skills between sessions. At the end of the online sessions there was a final Skype session, with the therapist, to encourage participants to set long-term goals, discuss the treatment, and suggestions for improvements. Thus, there was a total of 10 treatment sessions (two Skype and eight online sessions).

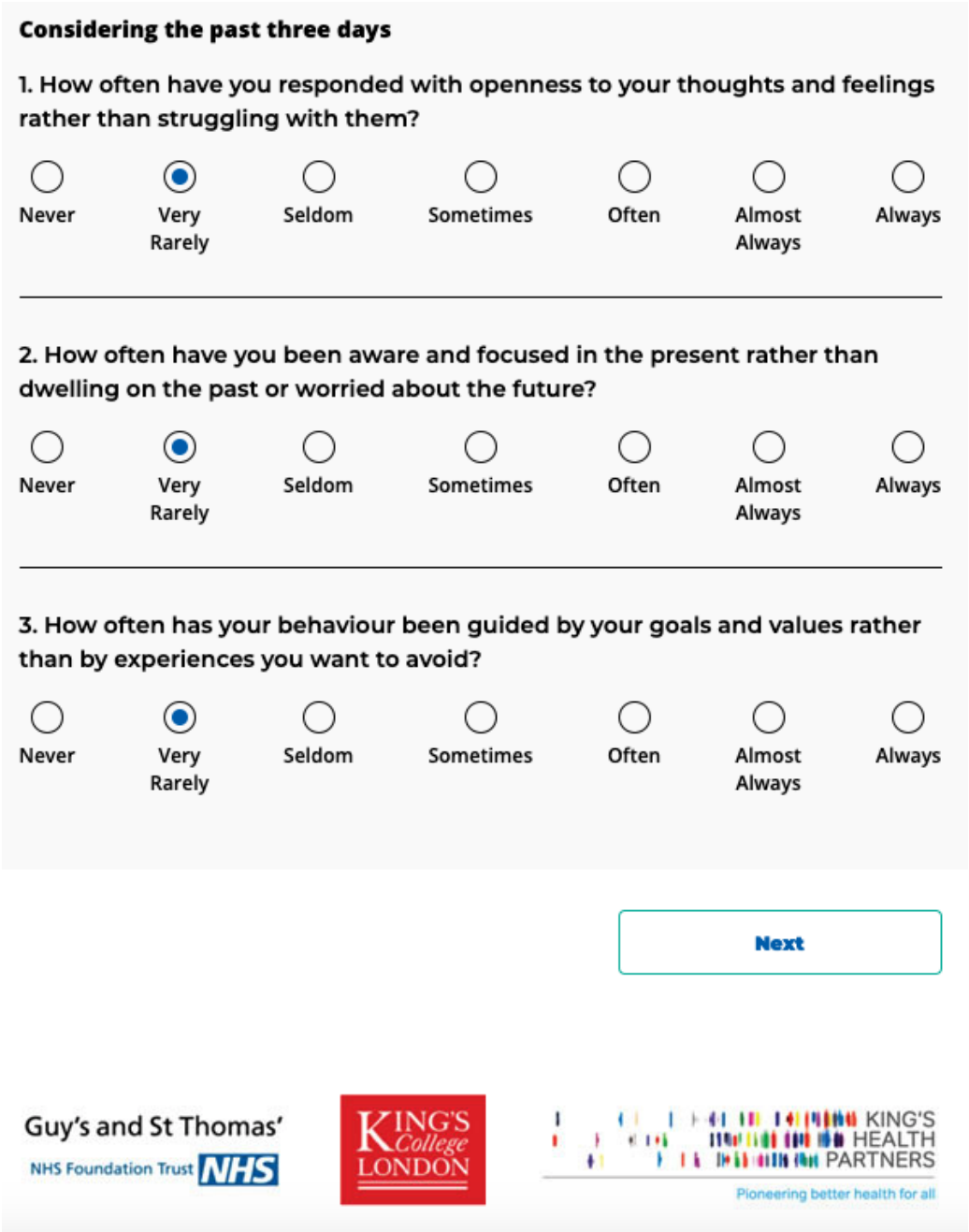

Figure 17: Ratings of developing skills as shown in ACT4PAIN platform

2.4 Assessment procedures

During baseline assessment, participants responded to self-report questions about diabetes and neuropathy duration, medication, comorbidities, age, sex, education, occupation, domestic status, and ethnicity. The participant self-report on the DN4i was used as a screen to support the potential diagnosis of PDN (Bouhassira, Lantéri-Minet, Attal, Laurent, & Touboul, 2008). The DN4i is a psychometrically validated tool used to screen for the possible presence of neuropathic pain. It includes seven interview questions, and a positive screen is indicated by the score of $\geq$3. The questions include (a) pain characteristics (e.g., burning, electric shocks) and (b) associated symptoms (e.g., tingling, numbness) (Bouhassira et al., 2008). This measure demonstrated good internal consistency in the current sample (Cronbach's α= 0.72). For participants recruited from the NHS there was also physicians' diagnosis for diabetes and PDN.

2.5 Primary feasibility outcomes

The primary feasibility outcomes for this study included recruitment, retention, treatment completion rates, and data completeness. Feasibility thresholds for these were defined *a priori*. The targeted sample to recruit was 30 participants. The aim was to achieve a follow-up questionnaire completion rate of 80% and a treatment completion rate of 70% (Scott et al., 2018b). The online treatment completion was calculated as the proportion of participants who completed the treatment, defined beforehand, based on Scott's at al. (2018) feasibility study, as participants completing at least 7 out of 10 sessions. Thus, recruitment of 30 participants, and achieving 80% follow-up questionnaire completion and 70% treatment completion would support the feasibility of a fully powered RCT.

2.6 Secondary outcomes

Secondary to the primary feasibility aims outlined above, this study aimed to produce estimates of the magnitude of treatment effect on standard pain outcomes and PF treatment processes as

preliminary assessment of potential efficacy. All clinical outcomes were assessed with psychometrically validated and reliable instruments.

2.6.1 Standard Pain Outcomes

Pain intensity and Pain distress: Pain Scale

Participants rated their average overall pain intensity and distress now and during the past week on a 0-(no pain/distress) 10 (worst possible pain/distress) numerical scale (Von Korff et al., 1992). This measure has been validated in people with general chronic pain (Jensen et al., 1999).

Depression Symptoms: Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a widely used measure of depression symptoms. It is a 9-item questionnaire rated on a 0-3 numerical scale, with the last item rated from 'not difficult at all' to 'extremely difficult'. A higher score for the sum of the 9 items indicates higher levels of depression severity (Kroenke et al., 2001). This measure demonstrated good internal consistency (Cronbach's α= 0.88) in the current sample.

Functional Impairment: Work and Social Adjustment Scale (WSAS)

The WSAS is a five-item questionnaire assessing functional impairment related to one's health condition. It has been previously used in chronic pain trials (Scott et al., 2018b) and focuses on domains of functioning such as work and hobbies that might be targeted within the treatment. Each item is rated on a 0 (no impairment) to 8 (very severe impairment) scale (Mundt et al., 2002). This measure demonstrated good internal consistency (Cronbach's α= 0.94).

Patients' Global Impression of Change (PGIC)

The PGIC is a single-item scale assessing participants' overall perception of change after treatment (Guy, 1976). On this scale participants report their change as very much improved, much improved,

minimally improved, no change, minimally worse, much worse, or very much worse. It is routinely used in trials for chronic pain (Scott & McCracken, 2015).

2.6.2 Theoretically-relevant treatment process variables

Chronic Pain Acceptance: Chronic Pain Acceptance Questionnaire (CPAQ-8)

The CPAQ-8 is a reliable measure of chronic pain acceptance on a scale from 0 (never true) to 6 (always true). The measure reflects pain willingness and activity engagement in the context of pain (Fish et al., 2010; McCracken et al., 2004). This measure demonstrated good internal consistency in the current sample (Cronbach's α= 0.81).

Cognitive Fusion: Cognitive Fusion Questionnaire (CFQ-7)

The CFQ-7 is a measure of cognitive fusion or defusion with items rated on a 1 (never true) to 7 (always true) point scale (Gillanders et al., 2014). Cognitive defusion, is the capacity to experience thoughts as just thoughts, and not as events as they are directly experienced. This measure demonstrated good internal consistency (Cronbach's α= 0.97).

Committed Action: Committed Action Questionnaire (CAQ-8)

The CAQ-8 is a measure of committed action as defined in the PF model (McCracken et al., 2015). Its items are rated on a 0 (never true) to 6 (always true) scale and they reflect the level of flexible commitment in the pursuit of meaningful goals, and plans. This measure demonstrated good internal consistency (Cronbach's α= 0.86).

Self-as-context: Self-Experiences Questionnaire (SEQ)

The SEQ, assesses self-related processes in the PF model, mostly including the capacity to see oneself as distinct from one's thoughts and feelings. The SEQ is a 15-item questionnaire in which items are

rated on a 0 (never true) to 6 (always true) numerical scale (Yu et al., 2016). This measure demonstrated good internal consistency (Cronbach's α= 0.95).

3. Statistical Analyses

Data was analyzed with the Statistical Package for Social Science for Windows (version 18.0 IBM, SPSS). Descriptive statistics, including means and standard deviations (SDs) for continuous variables and frequencies and percentages for categorical variables, were calculated for participant characteristics and primary feasibility outcomes.

For the clinical outcomes and process variables, including pain distress and pain intensity (pain scale), depression symptoms (PHQ-9), functional impairment (WSAS), chronic pain acceptance (CPAQ-8), cognitive fusion (CFQ-7), committed action (CAQ-8), and self-as-context (SEQ), *t*-tests were conducted to determine whether there were differences on the baseline scores for these variables between completers and non-completers of the treatment. The secondary aim of the study was addressed via effect size calculations and paired t-test analyses to examine the magnitude of the effect over time on these measures within the single group receiving treatment. In exploratory analyses, mixed between groups and repeated measures ANOVA were used to examine whether treatment completion status was associated with any effects on the measures. The final set of frequency analyses addressed descriptively the participant's perception of treatment change (PGIC).

Clinically meaningful changes were also calculated following the IMMPACT recommendations, which includes the convention of applying a threshold of 1/2 SD (Dworkin, McDermott, Farrar, O'Connor, & Senn, 2014). The value for 1/2 SD was calculated for each outcome for the whole sample at baseline (pre-treatment). A clinically significant effect was identified where the change observed for a participant, in a specific outcome, exceeded 1/2 SD between pre- and post-treatment.

4. Results

4.1 Sample Characteristics

The mean age of participants was 51.23 (SD= 13.30) years. Men represented 56.7% of the sample and the sample was predominantly white (67%). Equal proportions of the sample were either in full-time employment (30%), or unemployed due to pain (30%), while about a quarter were retired (23.3%).The median DN4i score of all participants was 4.00 and all participants scored higher than the cut-off (an overall score of at least 3) for neuropathic pain (Timmerman et al., 2017). The mean duration of PDN was 6.97 years (SD= 1.04). Please see Table 19 and 20 for detailed demographic and clinical characteristics.

Table 19: Sample demographic characteristics (N=30)

	N (%) or M (SD) or Median (Range)
Age (years)	51.23 (13.30)
Age range 21 to 50 years	15 (50%)
Age range 51 to 80 years	15 (50%)
Education (years)	15.20 (4.92)
Gender	
Male	17 (56.7%)
Female	13 (43.3%)
Ethnicity	
White	26 (86.6%)
Asian	2 (6.7%)
Mixed	2 (6.7%)
Living status	
Alone	5 (16.7%)
With partner	10 (33.3%)
With child/children	2 (6.7%)
With partner and child/children	8 (26.7%)
With other relatives	3 (10%)
With friends/flatmates	2 (6.6%)
Employment status	
Employed full time	9 (30%)
Employed part time	3 (10%)
Unemployed - due to pain	9 (30%)
Unemployed - unrelated to pain	1 (3.3%)
Student/Training - full time	1 (3.3%)
Retired	7 (23.3%)
Diagnosis of type 1 Diabetes	12 (40%)
Diagnosis of type 2 Diabetes	18 (60%)
DN4i	3.5 (0.00-7.00)
≥4	30 (100%)

Note: N is the number of participants, % is the percentage the number of participants represents in the sample, M is the mean and SD is the standard deviation. Range reveals the lowest and highest value, respectively.

Table 20: Diabetes and Pain characteristics (N=30)

	N (%) or M (SD)
Diabetes diagnosis (years)	15.50 (2.39)
Painful diabetic neuropathy duration (years)	6.97 (1.04)
Analgesic Medication	
Non-steroidal anti-inflammatory drugs	4 (13.3)
Anticonvulsants	3 (10.0)
Anti-depressants	14 (46.7)
Anti-epileptics	7 (23.3)
Opioids	8 (26.7)
Other	6 (20.0)
No analgesic drugs	5 (16.7)
Comorbidities	
Retinopathy/Vision impairment	11 (36.7)
Cardiac infarction	2 (6.7)
Angina pectoris	1 (3.3)
Coronary stent	2 (6.7)
Coronary bypass	2 (6.7)
Diabetic nephropathy	13 (43.3)
Dialysis	1 (3.3)
Leg/Foot ulcer	3 (10.0)
Operation on legs	3 (10.0)
Amputation	1 (3.3)
Sleeping disorders	13 (43.3)
Micturition and defecation disorder	2 (6.7)
No comorbidity	7 (23.3)

Note: N is the number of participants, % is the percentage the number of participants represents in the sample, M is the mean and SD is the standard deviation.

4.2 Primary Feasibility Outcomes

In total of 225 people were referred or expressed initial interest in the study and 30 of these consented to participate (24.6% recruitment) during a three-month recruitment period. 122 (54%) declined to participate and 73 (32%) were not eligible. Participants were recruited from Guy's and St Thomas NHS Foundation Trust (n=2) and online advertisements (n=28), between October 2018 to December 2018. Twelve (40%) participants completed the online treatment sessions as per the specified completion definition. All participants were retained in the study (100%), in the sense that they completed all measures, and data completeness was 100%. Reasons for discontinuing treatment can be found in Figure 14. For the 18 people who did not complete treatment the most frequent reasons were no adequate time (44.4%, n=8), other health problems (22.2%, n=4), computer problems (10.5%, n=2), or other (22.9%, n=4).

Analyses of pre-treatment data for pain intensity and pain distress variables revealed no significant differences between treatment completers and non-completers. However, comparison of pre-treatment scores for depression symptoms, functional impairment, chronic pain acceptance, cognitive fusion, committed action, and self-as-context variables showed large differences between completers and non-completers. It is notable that, at pre-treatment, treatment completers demonstrated lower cognitive fusion and functional impairment, and higher levels of committed action, self-as-context and acceptance than non-completers. Please see Table 21 for more details.

Table 21: Baseline scores on study variables for treatment completers and non-completers

	Completer	N	Mean	SD	*t*	*d*	p-value
Pain intensity (Rating Scales)	Yes	12	6.50	1.58	0.497	0.19	0.623
	No	18	6.13	2.15			
Pain distress (Rating Scales)	Yes	12	6.16	2.50	-0.334	-0.13	0.741
	No	18	6.47	2.43			
Depression symptoms (PHQ-9)	Yes	12	11.16	7.28	-2.341	-0.87	0.027
	No	18	17.00	6.27			
Functional impairment (WSAS)	Yes	12	15.92	12.29	-2.033	-0.76	0.052
	No	18	25.44	12.76			
Cognitive fusion (CFQ-7)	Yes	12	11.83	9.31	-2.133	-0.80	0.042
	No	18	21.17	13.08			
Committed action (CAQ-8)	Yes	12	33.17	8.48	2.368	0.88	0.025
	No	18	25.17	9.42			
Self-as-context (SEQ)	Yes	12	64.33	16.77	1.942	0.72	0.062
	No	18	52.28	16.58			
Chronic pain acceptance (CPAQ-8)	Yes	12	26.08	5.40	2.973	1.11	0.006
	No	18	19.61	6.11			

Note: On pain intensity, pain distress, depression symptoms variables a higher score means worse well-being/functioning, while higher scores on process variables (except cognitive fusion measure) indicate higher PF.

4.3 Secondary Feasibility Outcomes: Clinical Outcomes

At post-treatment, all of the 18 treatment non-completers (60% of the overall sample) reported "no change" in their health and functioning compared to before treatment. Amongst treatment completers (N=12) all reported that they felt 'improved' (N=10) or 'very much improved' (N=2).

Each of the variables from the clinical outcome and process measures was examined for normality using histograms, Q-Q plots, skewness and kurtosis. None of these showed significantly skewed

distributions or outliers expected to adversely affect the analyses. See Table 21 for each group means and standard deviations on study variables.

Effect size calculations and paired t-test analyses of pre- and post-treatment scores for the full sample revealed small effects over time for depression symptoms and functional impairment, and medium effects for pain intensity and pain distress, chronic pain acceptance, cognitive fusion, committed action, and self-as-context. These results include a mix of improvements in some variables and deterioration in others, owing particularly to deterioration in the larger treatment non-completers (Table 21). However, the majority of the sample did not complete treatment and, therefore, an improvement in the full sample analysis was not necessarily expected. The analysis of time by completer, which was conducted, shows that some of these variables improved among the completers.

4.4 Exploratory Analyses of Treatment Completion and Clinical Outcomes

Large interaction effects between time point and treatment completion were observed across all variables examined except for chronic pain acceptance where the effect was very small. The large effects included pain intensity, pain distress, depression symptoms, functional impairment, cognitive fusion, committed action, and self-as-context.

This was confirmed when data was split into completers and non-completers of the treatment. For completers there were significant improvements within group over time, including a large effect for pain intensity and pain distress, depression symptoms, and functional impairment. These results appear superior to those who did not complete the treatment who generally deteriorated.

Over time completers improved and demonstrated a large effect for committed action compared to non-completers who had lower scores and a similarly large effect in the opposite direction. Completers showed a medium effect for cognitive fusion and self-as-context. On the other hand, non-completers over time reported significantly higher levels of cognitive fusion and lower levels of

self-as-context. There were medium effects for completers and non-completers for chronic pain acceptance. Please see Table 22 for more details.

4.5 Clinically Meaningful Changes

The percentage of completers and non-completers who experienced clinically meaningful changes can be found in Table 23. At post-treatment, the majority of treatment completers showed meaningful improvements for 7 out of 8 of the outcome variables. The exception was chronic pain acceptance, where 41.7% meaningfully improved while 50% did not meaningfully change. Very few of the completers deteriorated meaningfully, for 4 of the outcomes this was none, and for the others this was one participant. For the non-completers the picture of meaningful change was more mixed, in 6 of 8 outcomes 72% or more of the participants showed either no meaningful change or they meaningfully deteriorated. For just two outcomes the majority meaningfully improved, for committed action and self-as-context, which was unexpected. For pain intensity, pain distress, and depression, the majority of non-completers deteriorated.

Table 22: Paired t-test uncontrolled analysis and repeated measures ANOVA examining psychological flexibility variables (N=30)

Paired t-test uncontrolled analysis							
	Pre-treatment scores		Post-treatment scores				
	Mean	SD	Mean	SD	*t*	*d*	*p-value*
Pain intensity	6.28	1.92	5.05	3.64	1.59	0.42	0.124
Pain distress	6.35	2.42	5.28	3.88	1.29	0.32	0.208
Depression symptoms	14.67	7.187	14.27	9.00	0.26	0.05	0.795
Functional impairment	21.64	13.24	22.67	15.91	-0.34	-0.07	0.736
Cognitive fusion	17.43	12.44	24.87	15.15	-2.58	-0.53	0.015
Committed action	28.37	9.76	22.50	15.71	2.23	0.44	0.034
Self-as-context	57.10	17.43	39.53	29.37	3.41	0.72	0.002
Chronic pain acceptance	22.20	6.58	24.00	4.15	-1.74	-0.32	0.092

Time*Completer interaction effects									
		Pre-treatment scores		Post-treatment scores					
	Completer	Mean	SD	Mean	SD	MS	*F*	d_{ppc2}*	*p-value*
Pain intensity	Yes	6.50	1.58	0.83	0.72	196.54	82.89	3.76	0.000
	No	6.13	2.15	7.86	1.17				
Pain distress	Yes	6.16	2.50	0.75	0.45	189.23	48.29	2.93	0.000
	No	6.47	2.43	8.31	1.19				
Depression symptoms	Yes	11.16	7.28	4.08	3.23	446.67	21.94	-1.65	0.000
	No	17.00	6.27	21.06	3.06				
Functional impairment	Yes	15.92	12.29	3.92	3.32	1698.68	20.55	-1.71	0.000
	No	25.44	12.76	35.17	3.33				
Cognitive fusion	Yes	11.83	9.31	7.17	2.62	1464.10	19.19	-1.08	0.000
	No	21.17	13.08	36.67	4.33				
Committed action	Yes	33.17	8.48	40.25	5.15	1677.03	35.26	2.36	0.000
	No	25.17	9.42	10.67	5.78				
Self-as-context	Yes	64.33	16.77	73.42	7.90	7102.23	44.44	2.64	0.000
	No	52.28	16.58	16.94	8.98				
Chronic pain acceptance	Yes	26.08	5.40	28.33	2.27	2.03	0.12	-0.13	0.729
	No	19.61	6.11	21.11	2.00				

Note: *d_{ppc2} (pretest-posttest-control): according to Morris (2008).

Table 23: Percentages of completers and non-completers who made clinically meaningful improvements, showed no change and deteriorated at post-treatment

	Completers (N = 12)			**Non-completers** (N = 18)		
	Improved (%)	No change (%)	Deteriorated (%)	Improved (%)	No change (%)	Deteriorated (%)
Pain intensity	12 (100.0)	0 (0.0)	0 (0.0)	2 (11.1)	4 (22.2)	12 (66.7)
Pain distress	12 (100.0)	0 (0.0)	0 (0.0)	3 (16.7)	4 (22.2)	11 (61.1)
Depressive symptoms	8 (66.7)	4 (33.3)	0 (0.0)	2 (11.1)	6 (33.3)	10 (55.6)
Functional impairment	7 (58.3)	5 (41.7)	0 (0.0)	1 (5.6)	10 (55.6)	7 (38.9)
Cognitive fusion	5 (41.7)	6 (50.0)	1 (8.3)	1 (5.6)	4 (22.2)	13 (72.2)
Committed action	8 (66.7)	3 (25.0)	1 (8.3)	16 (88.9)	0 (0.0)	2 (11.1)
Self-as-context	7 (58.3)	4 (33.3)	1 (8.3)	18 (100.0)	0 (0.0)	0 (0.0)
Chronic pain acceptance	5 (41.7)	6 (50.0)	1 (8.3)	5 (27.8)	7 (38.9)	6 (33.3)

Note: Percentages are rounded up to 1 decimal digit.

5. Discussion and Conclusions

The aim of this study was to assess the feasibility of conducting a larger RCT of online ACT for people with PDN. The targeted sample size was recruited (N= 30), all participants were retained in the study and completed follow-up questionnaires. However, the treatment completion rate was 40%, which was below the prespecified feasibility target of 70%. Hence, partial feasibility was found for the research and treatment methods for evaluating online ACT for PDN in a larger RCT. However, the treatment completion rate here is considered inadequate to justify proceeding to a full-scale trial until some modifications to enhance treatment engagement are designed and demonstrated.

The treatment completion rate for the current treatment was 40%, which is lower than a Dutch trial (72%) (Trompetter et al., 2014), a German trial (60%) (Lin et al., 2017), and a UK trial (61%) (Scott et al., 2018b) of online ACT for general chronic pain. In the current study, there were differences at baseline between treatment completers and non-completers, even though the sample was largely self-selected online, and these differences may underline the high drop-out rate. Particularly, non-completers had relatively higher levels of cognitive fusion, depressive symptoms, functional impairment, and lower levels of committed action, pain acceptance and self-as-context. This appears not to have been found in other similar studies (Lin et al., 2017; Scott et al., 2018b; Trompetter et al., 2014) and may be unique to the PDN population, perhaps due to the complexity or nature of neuropathic pain, or it could be due to some unique aspect of the setting or methods used here. As this is a one time finding in a small sample it is too soon to determine what it means.

If further research again shows that factors such as higher levels of cognitive fusion, depressive symptoms, functional impairment, and lower levels of committed action, pain acceptance and self-as-context, are associated with inadequate treatment completion, then they could be used either in selectively allocating participants to treatment, as targets for pre-treatment intervention, or as a

basis for redesign of the treatment methods or content. Presumably selecting participants with relatively lower depression or functioning impairment as a group may show better completion rates.

It may be that participants with particularly low levels of PF, or severe depression and high pain interference, may require more intensive psychological therapy, such as that delivered in a face-to-face setting (individual or group). However, it is known from previous studies that online treatment completion rates can be low, apparently due to problems with the use of technology, barriers due to poor health, or low motivation (Simblett et al., 2018). Based on the current data, it is not known whether it was the ACT approach itself, aspects of online delivery, requirements inherent in any psychological treatment, or all the above, that were unacceptable to participants. Most of those who did not complete treatment reported a lack of time. Another possible explanation represented in supplemental background information was that 11/30 participants reported some degree of visual impairment, which would make it difficult for them to complete treatment which mainly consisted of videos. Each of these possibilities deserves further consideration.

Future research may also explore treatment engagement through a qualitative study to investigate PDN participants' preferences for delivery format and views about ACT as a treatment approach. The model underlying ACT suggests a core set of behavioural processes underlie the treatment impact and that a standard package of this treatment ought to be generally applicable. However, the current data suggest that the treatment may need to be better tailored in a PDN context. This could be achieved by providing specific case examples of PDN throughout and orienting participants to problem areas specific to PDN such as fear of falling (Geelen et al., 2017; Kioskli et al., 2019). Treatment might also focus more explicitly on improving sleep. Given that 13/30 of the participants reported significant sleeping problems, this could be a motivating element if added to the treatment. A qualitative study could help to further identify specific problems area within PDN for which to apply ACT skills. This could contribute to better tailoring the treatment for this population and enhance engagement.

Another way to potentially enhance treatment engagement is to allow the treatment to be more dynamically customizable around each individual. This could include remotely assessing each case intensively over time, supporting the selection of treatment modules that are personalized, delivering only the modules particular participants need and not the ones they do not, leading to more rapid and efficient benefits from treatment (Fisher et al., 2019). In theory, a customized modular treatment guided by daily data gathering could pick up on, and intervene with, engagement lapses to promote better completion rates. The treatment components delivered here could certainly be repackaged to operate in this fashion.

The observed uncontrolled effect sizes on the clinical outcomes and process measures ranged from small to large at 3-months, favouring a decrease of depression symptoms, functional impairment, pain intensity and pain distress and an increase of chronic pain acceptance, and committed action, in treatment completers. Although clinical outcome results are highly preliminary, the large reduction in pain differs from other ACT trial results. This may be relevant to the observation in a recent cross-sectional survey which suggested that PF may play a smaller role, compared to pain intensity, in relation to distress and disability in the PDN population (Kioskli et al., 2019). It could also be related to the severity of participants' PDN, and this is not adequately measured in this study.

The rate of clinically meaningful results for treatment completers, across outcomes, are encouraging. At post-treatment, all treatment completers showed meaningful improvement in at least 3 variables, 83.3% in at least 4 variables, 41.7% in at least 5, 33.3% in at least 6, 25% in at least 7 and 16.7% in 8. On the other hand, all non-completers showed a meaningful deterioration in at least 2 variables, and half of non-completers deteriorated in at least half (4 of 8) of the outcomes. These results may provide "proof of concept" that ACT can benefit people suffering effects of PDN provided that they can be supported to complete the treatment sessions. On the other hand, support for applying ACT in this context may only apply for people who are relatively higher in functioning and PF.

A notable result is the number of clinical outcome and process measures on which those who did not complete treatment worsened during the three-month interval examined. In fact, on every measure with the exception of pain acceptance, the non-completers were worse at the end of the study compared to the beginning. In several cases these declines were significant and large, and in all cases this was unexpected. This perhaps reflects natural variability in PDN, and perhaps this contributed in some way to non-completion, but this is only speculation (Simblett et al., 2018; Soucy et al., 2018). Another possible explanation might be that the treatment did not adequately target key areas of need for participants. For example, depression is highly prevalent in people with diabetes and in those with diabetes complications as well. Therefore, not only does this population have significant levels of pain, but also have co-morbid disability because of PDN, like balance and mobility problems, and associated micro-vascular comorbidity, such as retinopathy and nephropathy (Anderson et al., 2001). These co-morbidities were not adequately measured or reported for this sample. Qualitative interviews with the non-completers would have allowed us to determine the reason of these changes and the main reason for discontinuing treatment. Also, a revised version of treatment might help participants to practice applying these skills more broadly to other diabetes related problems, which might be considered to have a larger impact on their functioning and quality of life.

Possibly, non-completers were experiencing symptoms of PDN during their engagement in this treatment, became more conscious of their experienced difficulties, and were willing to report them. Additionally, it is possible that the nature of neuropathic pain is responsible for non-completion of treatment. It may be relevant that neuropathic pain is different pathophysiologically, compared to other chronic pain conditions, with the dominant component of neuroplastic changes within the nervous system (Costigan et al., 2009). These speculations deserve study.

In this study, the most commonly suggested refinements by the non-completers, coming from comments in the experiential exercises or the last Skype session with the therapist, were to shorten audios and videos, add more face-to-face sessions, more educational material on diabetes and

neuropathy, and provide additional printed materials to supplement the online content. We note however that the total time for all online content was just 150 minutes, or an average of less than 19 minutes for each online session. Nonetheless, it could be possible to provide choices around longer exercises, by more clearly alerting participants regarding the length and providing them with scheduling options (now or later when there is more time available), or by providing a choice for several shorter exercises in the place of a lengthy one. A missed opportunity here, to investigate treatment non-completion, would have been to include in-depth exit interviews with participants who dropped out. Unfortunately, these methods were not possible in the current study due to lack of resources. Such a study could provide more detailed feedback on reasons for dropping out or losing interest.

This study has several limitations. Firstly, the study design does not allow for causal interpretations for observed changes in outcomes since this was not an RCT. Secondly, even though the recruitment was reached target (N=30), this is a small sample with high drop-out rates (60%), which may lead to limited reliability and precision of our estimates, and limited power for all of the mean comparisons. The sample was also too small to conduct meaningful analyses to identify characteristics associated with a favourable response to treatment responses. Thirdly, the fact that participants were self-selected to take part in the treatment means that results may not generalise to the wider population of people with PDN in need of treatment. Also, since the majority of participants were recruited from online portals, and even though we used the DN4i and self-reported questions for diabetes and PDN diagnosis, there is the possibility that participants did not fulfil more stringent diagnostic criteria for PDN. It is worth noting that this treatment applied here was designed for people with chronic pain in general. This is possibly not an ideal test for the specific feasibility for people with PDN, and a more tailored version of treatment may be ultimately more feasible. Unfortunately, at the time of this study there were no resources available to modify the available treatment to the population of

interest here. Finally, it is recognised that a different sample and longer follow-up may yield different results. The generalisability and reliability of the results still need to be established.

Despite these limitations, this is the first feasibility study of online ACT in people with PDN. Based on low completion rates a larger RCT testing efficacy is not feasible for the current online ACT treatment as examined here. Future research is encouraged to specifically address the problem of low treatment completion, possibly including active patient involvement and qualitative work. Further tailoring of research methods and treatment to specifically fit PDN may be needed. Another avenue, at the same time, is simply greater individualization. This could include identifying the defining features of individuals who will both engage and achieve clinically meaningful benefits from treatment model here, and those who will not. It could also include making this treatment more sensitive to whoever encounters it by breaking it into modules and personalizing the delivery of these based on assessment data.

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K.K., first author, responsible for the work, recruited patients, delivered the treatment, collected and analysed the data, and produced the first draft of the manuscript. L.M. and K.W. contributed to the conception, design of the study, and research plan, offered their guidance on protocol and assessment tools selection, edited approved the final version of the manuscript. W.S. contributed by offering guidance throughout the treatment delivery and statistical analysis plan, also revised, edited and approved the manuscript. E.G. supported the project and offered guidance and expertise, also revised, edited and approved the final version of the manuscript. The authors would like to also thank the diabetes clinic of Guy's and St Thomas Hospital, Diabetes UK, the pain forums and the participants for their help and support.

5.3 Summary

This study tested the feasibility of online ACT in people with PDN in the United Kingdom and evaluated whether a full-scale trial would be justified. In this single-arm trial, all participants were offered the online ACT program, and completed questionnaires at baseline and 3-month follow-up. Primary outcomes were recruitment, treatment completion, and retention rates. Secondary outcomes were within-groups effects on pain outcomes and PF evaluated through repeated measures ANOVA. Thirty participants took part in this study and 12 of them completed the treatment (40%), while all of them completed the baseline and follow-up questionnaires. Treatment completers reported lower levels of pain intensity, pain distress, depression symptoms and functional impairment and higher levels of committed action scores, compared to non-completers, at post-treatment. Results suggest that online ACT is only acceptable to a minority of participants, as indicated by low completion rates. However, among those willing to complete it, they may achieve benefit. Refinements to increase engagement are needed.

Chapter 6: General discussion

6.1 Chapter Overview

The purpose of this PhD project was to gain an understanding of Painful Diabetic Neuropathy (PDN), particularly from the perspective of the Psychological Flexibility (PF) model and, relatedly, examine the potential usefulness of Acceptance Commitment Therapy (ACT) for the treatment of PDN.

Three studies were carried out to this end: 1) a systematic review, 2) a cross-sectional survey, and 3) a small online feasibility intervention study. This research ultimately aimed to preliminarily test a prototype ACT-based treatment for people with PDN. The main research question was to determine whether the PF model and ACT could be used to improve the wellbeing of people with PDN.

This chapter will provide a general discussion of this set of studies and the wider implications of this work. This will be achieved through summarising the main results and evidence of each study, discussing the contribution of each study to the literature, and determining the potential theoretical and clinical implications. Furthermore, this chapter will discuss the limitations of the project as a whole and provide suggestions for future research.

6.2 Research Aims of the Thesis

This PhD thesis targeted to address the following research aims:

- Aim 1: To identify and systematically evaluate the evidence for the relationship between PDN and psychosocial factors (i.e. depression, anxiety) and the available psychological treatment trials in PDN (Study 1).
- Aim 2: To examine the relevance of PF to a sample of people with PDN in the UK (Study 2).
- Aim 3: To assess the feasibility of an online therapist-supported ACT treatment as applied to people with PDN and to provide recommendations for study progression (Study 3).

6.3 Summary of Main Findings

6.3.1 Study 1: A Systematic Review of the Literature of Psychosocial Factors and Psychological Interventions for Painful Diabetic Neuropathy

The first study of this thesis (study 1) systematically reviewed RCTs and observational studies and is described in Chapter 3. The study investigated the relationship between PDN and psychosocial factors (i.e. depression, anxiety) and synthesised the available evidence from psychological treatment trials in PDN. To date, there has been only one literature review investigating psychological factors in PDN. This earlier review focuses on the role of physical activity and coping strategies in relation to pain outcomes (Davies et al., 2015). The updated review reported here, was the first systematic review reviewing the status of psychosocial factors more broadly, including psychological treatments studies, in people with PDN. Despite the intended broader reach of the current review, results showed that the psychosocial factors investigated in the current studies remain limited, the evidence gathered is inconsistent, and there is a lack of high-quality RCTs. This led to the conclusion that there is an urgent need for the investigation of psychosocial factors in the context of PDN and for more psychological interventions to be tested, given that pharmacological treatments are in general of limited efficacy for the PDN population.

In this review, twenty-seven studies reflecting a mixture of cross-sectional and prospective studies (n=24) and RCTs (n=3) were included. There was moderate quality evidence with low risk of bias in 15, medium in 5 and high in 6 studies. Results revealed evidence of mostly consistent positive correlations between depression, anxiety, sleep disruption, low quality of life and pain outcomes in people with PDN with effect sizes ranging from small to large. Only one study examined fears (fear of hypoglycaemia, pain, fatigue, falling, negative evaluation and kinesiophobia) in relation to PDN and two additional studies measured acceptance of pain. Despite the number of studies, there was a lack of investigation of a broader range of psychosocial factors, that could be important in pain, such as

coping and PF. A need for more high-quality psychological research in PDN is evident. Particularly required are studies including trials of interventions with larger samples, better reporting, more robust trial designs, longer follow-up and higher treatment intensity. The absence of data from such studies currently limits our understanding of the role of psychosocial factors related to wellbeing and functioning in people with PDN.

A significant limitation of the current literature is that the variables examined in the previous studies lack a guiding and integrating a theoretical model. As a result, there is no sense of progress and our understanding is not developing. Further investigation of the understudied psychosocial factors of current theoretical interest, such as acceptance and PF more broadly, was suggested for future research. The potential value in the theoretical model of PF and ACT is that they are underpinned by clear assumptions and principles, include a model of wellbeing and performance, and link directly to a set of treatment methods already widely tested and gaining evidence (Ciarrochi, Bilich, & Godsell, 2010; Wersebe, Lieb, Meyer, Hofer, & Gloster, 2018). Hence, the PF model could contribute to the examination of psychosocial factors and application of an ACT-based treatment which may be of benefit for people with PDN.

The systematic review that was conducted for this PhD, to identify psychosocial factors, revealed findings which are partially consistent with the general chronic pain literature. More specifically, the most commonly identified factors were depression, anxiety, poor sleep, and low quality of life as in most studies of chronic pain conditions (Edwards, Dworkin, Sullivan, Turk, & Wasan, 2016; Jensen, Moore, Bockow, Ehde, & Engel, 2011). There is a wealth of evidence that these factors strongly contribute to long-term effects of pain such as mortality (Kadam, Thomas, & Croft, 2005; Smith, Wilkie, Uthman, Jordan, & McBeth, 2014), disability (Hall et al., 2011; Hung, Liu, & Fu, 2015) and increased healthcare costs (Baumeister, Knecht, & Hutter, 2012). However, factors commonly assessed in the chronic pain literature such as coping, beliefs, and social factors have not been studied in the PDN literature.

6.3.2 Study 2: A Cross-Sectional Survey of People Suffering from Painful Diabetic Neuropathy

To build on the results from the systematic review (Chapter 3), a quantitative cross-sectional survey study (study 2) was undertaken, as described in Chapter 4. This study was designed to examine the relevance of PF in a sample of people with PDN in the UK (n=225). The sample was recruited from online advertisements (n=213) and hospital services (NHS; n=12). Recruitment was more successful from online advertisements and less successful from the NHS clinics, although overall the recruitment target (n=200) was achieved and surpassed (n=225). Results from correlational analysis suggested that acceptance of pain was negatively correlated with pain intensity, pain distress, functional impairment, depression severity, and depression impact. Cognitive fusion was positively correlated with pain intensity, functional impairment, depression severity, and depression impact. Committed action was negatively correlated with functional impairment, depression severity, and depression impact. Results from regression analyses suggested that the variables representing PF accounted for significant variance in all the equations for key outcomes except for pain distress. However, pain intensity demonstrated larger correlations with these same outcomes. These results suggest that PF does play a role (accounting for 6.8% of variance), however, it may not play such a significant one, as pain intensity (accounting for 32.2% of variance) in people with PDN compared to the general chronic pain population. However, it is important to note that psychological treatments do not directly target the reduction of pain intensity, but behaviour change or emotional regulation, which can affect perceptions of pain, and therefore addressing PF through ACT treatment seemed appropriate. Reliability and generality of these results remain to be determined, and it is possible these results could differ if recruitment from NHS settings was more successful.

To date, this is the first and only investigation which has provided preliminary evidence for the relevance and potential applicability of the PF model in a PDN sample. Therefore, treatments aimed to enhance PF (i.e. ACT) may be suitable and require testing. Results of this survey should facilitate further investigations in this field.

6.3.3 Study 3: Internet-Based Feasibility Study of Online Acceptance and Commitment Therapy for People with Painful Diabetic Neuropathy

Based on the findings of the systematic review and cross-sectional survey, a previously developed online therapist-supported ACT treatment was provided to people with PDN, as described in Chapter 5. This single-arm study (study 3) tested the feasibility of treatment and trial methods and investigated the impact of ACT on pain and functioning in people with PDN. The recruitment for this study was conducted online and from hospital services (NHS), and it was successful overall since the targeted sample size was achieved (n=30). However, online advertisements proved much more successful (n=28) than NHS recruitment (n=2). All participants completed follow-up assessments. Thus, study retention was 100%. On the other hand, treatment completion was only 40%, which was below the prespecified feasibility target of 70%, suggesting limited feasibility in this regard.

This was the first study applying ACT in a PDN population and currently one of the six studies, in total, applying any type of psychological intervention to people with PDN. Since the publication of the systematic review that was conducted for this PhD, two additional studies have been identified (Hussain & Said, 2019; Nathan et al., 2017). None of these psychological interventions involved ACT. Both of the recent additional studies showed that participants who completed the psychological treatments (including Mindfulness-based stress reduction, Mindfulness-based meditation, Progressive Relaxation Meditation) reported improvement in pain interference, among other outcomes. These results are concordant with the secondary outcomes results from the feasibility study conducted for this PhD.

This feasibility study provided preliminary evidence for the potential benefit of ACT treatment in people with PDN. However, the small sample size means the results lack generalisability. More specifically, all treatment completers reported that they felt ‘improved’ or ‘very much improved’, overall, after treatment. However, since there were differences between completers and non-

completers at baseline, it is not certain that this improvement was attributable to the treatment received. Future studies are required to develop a treatment more specific to people with PDN, to make refinements in the delivery method and materials used or test other approaches as well. Further investigation on ways to reduce drop-out rates and how to tailor the intervention more precisely to this population is needed.

6.4 Theoretical Implications

This project informs potential future developments of the PF model. The cross-sectional survey indicated that for people with PDN, PF processes explained much less of the variance in predicting functional impairment than pain intensity did. This contrasts with studies investigating the PF model in other pain conditions. More specifically, a study of 384 people with general chronic pain, aiming to explore the relative magnitude of change in PF processes associated with ACT, showed that in regression analyses the change in PF processes explained 6-27% of the variance in depression and functioning changes (Scott, Hann, & McCracken, 2016). Other studies (McCracken et al., 2015; Scott & McCracken, 2015; Vowles & McCracken, 2008) have demonstrated that changes in pain acceptance are associated with improvements in treatment outcomes, which was not evident in our study. It appears that the variance accounted for, by PF, in terms of pain-related functioning is smaller in PDN than other pain samples.

It should be taken into consideration that neuropathic pain differentiates mechanistically, compared to other chronic pain conditions, due to its domination of the maladaptive plasticity within the nervous system (Costigan, Scholz, & Woolf, 2009). Pain hypervigilance could be the reason that pain intensity plays a more important role than PF. Hypervigilance has been defined as “a behaviour involving enhanced or exaggerated search of environmental stimuli or scan for threatening information (pp.183-184)” (Rollman, 2009). It has been suggested that pain-related information may contribute to the aggravation of pain experience (Herbert et al., 2014). Evidence has been found in

people with fibromyalgia, that a context of pain or threat lead to hypervigilance and patients may experience more pain (Rost, Van Ryckeghem, Schulz, Crombez, & Vögele, 2017).

This could also be due to biomedical features, for example, the unique burning pain associated with PDN which may be more important. On the one hand, there is the possibility that features of neuropathic pain, and how it is experienced psychologically, may modify the role of other psychological processes and their relationship with physical functioning. It should also be noted that people with DM experience many comorbidities and PF may not suffice, so a broader range of factors should be examined. On the other hand, the discrepancies between the results of this thesis, and the role of PF in other pain samples, may have occurred because a selected or non-representative sample of participants was obtained.

Furthermore, the impact of diabetes self-management should also be considered. An RCT delivered ACT or education alone to 81 participants with diabetes (Gregg, Callaghan, Hayes, & Glenn-Lawson, 2007). Results showed that participants who received ACT were more likely to cope with stressful diabetes-related thoughts and keep their HbA1c within the target range. This may indicate that the stability of diabetes management might influence the PF model's applicability to PDN outcomes. For example, if a person's diabetes is poorly managed (high glucose levels) this could be the biggest driver of pain and disability (Wagner, Reiser, & Lotz, 2006; Won, Park, Park, & Riew, 2009). However, once glycaemic levels are stable, it might be that psychological factors and the PF model are more relevant for PF outcomes. Of course, PF might play a role in a person's willingness to engage in behaviour patterns, such as lifestyle changes and glucose monitoring (Lindholm-Olinder et al., 2015).

PDN could also differ from other pain populations, due to the stabbing, stinging, burning sensation which results in sleep disruption and lower quality of life in general. There may also be the compounding influence of other diabetes complications and comorbidities, such as additional

microvascular complications, retinopathy and nephropathy which add to their level of disability (Colloca et al., 2017; Marchettini, Lacerenza, Mauri, & Marangoni, 2006).

PF is a transdiagnostic model and can be applied to various conditions with no need for any alterations (Dindo et al., 2017; Levin et al., 2014). PF has a core set of processes assumed to contribute to health and function across a wide range of health problems (Kashdan, 2010). Even when these PF processes are applied, this model does not always assure continuous healthy actions. The main criticism that the PF model and ACT have received is that there is not a distinctive difference with other psychological approaches, like CBT (Scott, McCracken, & Trost, 2014). It has also been indicated that ACT is not as developed and methodologically advanced as traditional CBT (Öst, 2008).

Besides the strengths and limitations of the PF model, the third study of this PhD project demonstrated that the completion rates were low and one of the main reasons may have been that the treatment was not specifically tailored for the PDN population, as it was developed for the general chronic pain population. The restriction of using a previously designed generic treatment is a limitation of this PhD project. Of course, it is also a legitimate path towards treatment development in the absence of resources to test a fully tailored version.

6.5 Clinical Implications

Much more could and should be done to enhance the development and application of psychological treatments for PDN in the UK and worldwide, as there are no effective treatments for pain in this population (Davies et al., 2015; Finnerup et al., 2015). The clinical implications emerging from this PhD are as follows:

1. There is evident difficulty to identify people with a diagnosis of PDN. This was demonstrated in studies 2 and 3 where NHS recruitment was challenging. Similar to other conditions PDN is not easily identifiable via electronic patient record systems. Although clinical codes exist, they are not necessarily routinely applied, which means it is more difficult to conduct electronic record searches (Hall, Morant, Carroll, Gabriel, & McQuay, 2013). This raises questions as to whether there is under-diagnosis of this condition.

2. This project suggests that psychological interventions designed to enhance PF for people with PDN in the UK may facilitate pain management and encourage better health and wellbeing. However, the results must be treated with caution due to the limitations of this project. It is possible that tailoring ACT in a pragmatic way may provide more benefits to participants with PDN. Specific treatment content alterations could be applied to refine the content of the audio and video recordings in a way that applies specifically to experiences of people with PDN. This could include information on prevention and treatment options and the main physical challenges these people face, such as diabetic foot, muscle cramps and weakness, pain in the extremities and sexual dysfunction (Belapurkar et al., 2018). This information could be delivered within ACT experiential exercises and metaphors (Shayeghian, Hassanabadi, Aguilar-Vafaie, Amiri, & Besharat, 2016), which would facilitate the treatment process (Hayes et al., 1999). More specifically potential adaptations could be, supplementary reading material at the end of each session related to the condition's and treatment's issues and age-related problems (Schmidt, van Loon, Vergouwen, Snoek, & Honig, 2018), modifying the language in the experiential exercises within the videos targeting individuals with diabetes, and/or add a session regarding the management of diabetes distress to achieve optimal results. Of course, qualitative work would be firstly recommended, prior to any adaptations, to explore the views and preferences of people with PDN.

3. This project did not investigate the potential impact of glycaemic control on pain in people with PDN. Therefore, psychological treatments for this population may also require an educational aspect

within the treatment, specifically focused on providing information about monitoring glucose levels. Patient education is of great importance to manage and control PDN (Bril, 2012; Javed et al., 2015). Managing blood glucose levels and investigating how they might interact with psychosocial factors to influence pain/disability in PDN seems to be relevant for future research, especially in terms of improving the effectiveness of an intervention. The design of such treatment may particularly fit the UK because of the difficulty in accessing pain management specialty centres, the lack of available trained psychologists, and the stigma that might be associated with psychological therapy (Knaak, Mantler, & Szeto, 2017; Lake, 2017).

4. Finally, whilst this project has highlighted the potential benefits of psychological treatments for PDN, a challenge here is that there may not be a large enough workforce that is adequately skilled to deliver tailored psychological treatments for this population. Therefore, online treatments such as ACT may help address this issue. Alternatively, first-line treatment providers, for example nurses and GPs, could enhance their training and education by becoming more psychologically skilled and use psychologically informed interventions (i.e. ACT, CBT, DBT, MBSR) to improve the functioning and wellbeing of patients.

   It is recognised that some of the clinical implications of this research depend upon making changes in policy, health care and education systems and it is difficult to make recommendations based on these preliminary results. However, smaller changes may start from the initial consultation within the primary care service and referral process. There is limited psychological treatment and support available and little that is specifically for people with diabetes (DUK, 2008). The Improving Access to Psychological Treatment (IAPT) service is the most widely available, but this focuses on common psychological problems such as anxiety and depression. However, an issue for this PhD project is the need to improve treatment engagement and completion. This could be achieved by considering making changes to the online ACT treatment by: 1) using different recruitment methods to identify people with PDN from NHS services, for example in primary and secondary settings, 2) modifying the

treatment content to be specific and applicable to people with PDN, and 3) incorporating a longer follow-up.

6.6 Limitations

This PhD thesis has a number of limitations.

- In the systematic review (study 1) there was the potential for publication bias, since it was possible that some studies were not identified because they may have not been published, not written in English, or not have been indexed in the searched databases. It would be worth including non-English studies and grey literature and updating the systematic review. Furthermore, two recent studies were not included.

- Recruitment for the cross-sectional survey (study 2) and the feasibility study (study 3) was conducted mainly online, which means it cannot be deemed to have produced a sample representative of the general PDN population. Even though there were efforts to recruit from hospital secondary care services, these attempts were not very successful. There are generally few people with PDN attending diabetes clinics, therefore, accessing this population by conventional approaches to trial recruitment is a challenge. It is recommended that people with PDN should be referred to specialised pain clinics (Pop-Busui et al., 2016), but even in these clinics relatively few people with PDN attend. It is recognised that if participants had been recruited in a different way the results may have differed. Further research is encouraged to investigate this and identify the best method of recruitment, such as recruiting over a larger geographical area and involving primary care settings.

- In the cross-sectional survey (study 2), the PF measures used included pain acceptance, cognitive fusion, committed action, and self-as-a-context. These measures have not been validated in the PDN population, even though they have been validated in other chronic pain populations. Therefore, it is possible that the instruments did not perform in the same manner in this population, and

participants' responses may have been different if the measures had been developed and validated specifically for them.

- In study 3, a single treatment group design was conducted, and the intervention has thus not been fully tested against a control condition in an RCT. Therefore, different study designs are needed, such as a large scale RCT, to investigate the causal impact of ACT and the mediating role of PF, or as an alternative single case experimental designs (SCEDs).

- Treatment completion rates were lower than expected (40%) (in study 3), which warrants further investigation. To improve completion, changes may be needed in research methods, in treatment delivery, including the therapist support component, or in the treatment content. However, as the studies presented were conducted as part of a PhD project, time and resources were limited.

- This PhD project did not employ qualitative methods. Qualitative methods would have been useful for hypothesis generation, in-depth data collection, process evaluation, and the input from people with PDN might have made the treatment more accessible and effective. Conducting interviews with participants could have taken place at the following time-points: before the survey in order to get feedback on the content, wording, and length of the questionnaires; before the delivery of the psychological intervention to assess the acceptability of the mode and content and, perhaps most importantly, after the intervention to identify reasons for continuation or discontinuation of the treatment. This type of data collection can be time intensive and may be influenced by multiple factors, including the interviewer's own presence and beliefs, as well as interviewing skill set, location of the interview and ability of the interviewee to express and articulate their experiences (Sutton & Austin, 2015). The reason why these interviews were not conducted was because this PhD aimed to look at the practical feasibility of an ACT-based intervention. In retrospect, looking at the high drop-out rate (60%) in the feasibility study, future research would benefit from using qualitative methods from both the participants' and therapist's perspective**.**

- This project would have benefitted from ongoing patient and public involvement (PPI) from people with diabetes and/or PDN. PPI was obtained prior to the research being funded by Diabetes UK but it was not continued in a structured way. The treatment delivery platform (ACT4PAIN) originally included a PPI group which guided the final version. PPI could have provided clear and effective benchmarks from patients, staff, carers and HCPs for subsequent treatment development and could have made the treatment more relevant and inclusive (Holmes et al., 2019). It is worth noting that while online delivery is advantageous to increase access, it is relatively costly to develop up front, which was a barrier to tailoring the feasibility study that was conducted as part of this PhD. As expected, the methods used, and studies conducted both provide some progress and suggest future work that can be done. However, the importance of this set of studies is that they provide some indication of the next steps required in the development of treatment for people with PDN.

- A framework to inform the implementation of this intervention was not used. However, the originally developed treatment (ACT4PAIN) used the Medical Research Council's framework (MRC; Craig et al., 2008), for development and implementation. The MRC framework recognises the importance of interventions being tailored to the context and not standardised (Campbell, Donner, & Klar, 2007), and the greater use of theoretical insights in development and evaluation (Hardeman et al., 2005; Shiell, Hawe, & Gold, 2008). The recently updated framework, provided by the MRC and NIHR, recognises that completion of all the stages is a lengthy, iterative process. The implementation and evaluation plan should be considered from the beginning of an intervention's conceptualisation (O'Cathain et al., 2019; Skivington, Matthews, Craig, Simpson, & Moore, 2018), and could have enhanced this PhD.

6.7 Future Work

This set of studies investigated psychological factors in PDN and empirically examined the role of PF within ACT in people with PDN. These studies have added new knowledge regarding the experience of pain and responses to treatment from people with PDN. The cross-sectional survey and the online feasibility study were early attempts to empirically and clinically investigate PF in people with PDN. Further investigations are needed to establish the generalisability of the results. The application of different techniques, measurements and methodologies are required for the evaluation of the PF processes. Further modifications of the ACT-based psychological treatment may be necessary. Studies including qualitative, RCTs, longitudinal designs, or SCEDs, building on evidence from the above conducted studies, could be useful. The studies presented in this thesis are unique and novel and there is hope that they will further the existing knowledge and contribute to the development of better, more accessible, treatments for people with PDN.

In general, different research methods may be used in the future to further elucidate the role of the PF model and ACT for people with PDN. For example, SCEDs or n-of-1 designs would allow more intensive observation and report of participants' proposed changes and specific treatment refinements. SCEDs can evaluate the effect of an intervention on a single person and a study can include multiple single cases, potentially each replicating the same or similar result based on designs using repeated measurements where each person provides their own baseline for comparison (Krasny-Pacini & Evans, 2018; Tate et al., 2013). N-of-1 designs including multiple crossover randomised and blinded trials conducted with one patient would enhance the internal validity (Kravitz, Duan, & Braslow, 2004; Kravitz et al., 2008). The feasibility study that was conducted only collected data at two time points (pre and post treatment). Single case designs or n-of-1 methods would provide more data points on fewer people (McDonald et al., 2017; Morley, 2017). As mentioned, this more intensive following of each individual case, can more rapidly reveal useful information about engagement challenges and potential strategies to address these.

Future studies are particularly encouraged to pursue qualitative work. Qualitative research has several benefits for theory and treatment development. It can uniquely expose features of the pain experience in ways that quantitative methods cannot. It can obtain input from the participants' own words and thus yield information the researcher did not or could not expect. The epistemological assumptions that qualitative research adopts reveal different information than quantitative work, and it can be used in parallel with quantitative research and provide a more holistic result (Osborn & Rodham, 2010). Qualitative studies provide a comprehensive understanding of the key factors that may influence behaviours (Bartholomew et al., 2016; Kok, 2014), which ultimately inform targeted intervention development. The use of qualitative methods has increased in informing healthcare decisions. Interviews are a powerful way to generate personal descriptions and understand someone's world. Purposive sampling of a chosen population allows for the exploration of the experiences and beliefs of the respondent and this can then guide intervention development (Al-Busaidi, 2008).

There are currently limited studies reporting qualitative work in participants following their participation in ACT-based treatments in chronic pain (Casey, Smart, Hearty, Lowry, & Doody, 2019; Thompson, Vowles, Sowden, Ashworth, & Levell, 2018). However, these studies are useful in providing a unique insight regarding peoples' views and perceptions of their pain and treatment experience. Adding qualitative work to this project could have achieved a better tailored psychological treatment before delivery, enhanced treatment completion, and could offer useful, detailed feedback for future alterations following treatment delivery. Qualitative work could also help to disentangle whether it was the treatment content itself or the online delivery format that led to inadequate treatment completion. This can inform whether change is needed to the content or delivery level (e.g., group-based, different treatment provider), or both.

Future research needs to assess the acceptability and improve the uptake of psychological interventions, investigate the effectiveness of the treatments and increase the evidence-base for

psychological interventions for people with PDN in the UK. A holistic framework such as the Theoretical Framework of Acceptability (TFA), in which participants' acceptability can be quantifiable via the overall rating of ethicality, affective attitude, burden, opportunity costs, perceived effectiveness, self-efficacy and intervention coherence could be used to guide this process (Sekhon, Cartwright, & Francis, 2017).

Furthermore, clinical and health psychologists with expertise in chronic pain management and health researchers will be required. Personalised adaptations of ACT-based treatments which will make the treatment tailor-made for each person, encourage engagement, reduce drop-out rates and improve overall outcomes appear to be needed. It may also be necessary to involve diabetes specialists to advise on modifications which address the potential impact of glycaemic control on PDN. Lastly, it would be useful to repeat the 3 studies presented in this PhD thesis in different healthcare settings. The data presented here has added knowledge regarding the application of psychological treatments in people with PDN in the UK. The availability of these studies will help to clarify the applicability and acceptability of psychological interventions for the PDN population in different settings and to provide a starting point for future investigation of treatment needs and preferences for individuals with PDN.

6.8 Epistemological Assumptions

This study aimed to explore the perspectives of individuals on PDN, by using a social constructionist epistemological position. Social constructivism stresses out the importance of social context and culture. The social and cultural construction of knowledge is evident, while individuals create meaning through relationships with others and there are several ways to understand a situation. It argues that societies have a significant influence on the interpretation of experiences, resulting in influencing the physical and emotional states (Kim, 2001). This project was not only set out to confirm whether contextual cognitive behavioural approaches were, or were not, feasible. This

research programme adopts a social constructionist epistemological position by accepting that the experiences of individuals are constructed by their beliefs, thoughts, and social world. It is significantly important to avoid judging when participants describe the pain management strategies they have tried or the physical and psychological impacts.

6.9 Researcher Reflections

In order to contribute to the body of PDN knowledge, I started this PhD aiming to work on a series of well-designed studies which would provide clear answers to the set research questions. The experience and skills I gained through this project will be invaluable in my future research career.

By spending a lot of time at diabetes and pain clinics at Guy's and St Thomas Hospital, I was able to develop my understanding of diabetes and PDN. Observing both the HCPs and the patients helped me gain an insight into the patients' experience, NHS procedures and PDN management. Delivering the online treatment, with the guidance and support from my supervisory team, I was able to have hands-on experience in ACT treatment, develop my skills as a therapist by managing expectations, setting goals and providing feedback on the experiential exercises.

Before starting this PhD, my attention to detail, critical appraisal of the literature and manuscript preparation were limited with room for improvement. Written feedback and comments and face-to-face meetings with my supervisory team helped me develop these important skills and encouraged me towards precision. Additional skills which I have gained are project management, data analysis, and presentation skills.

I wish I could have included an additional qualitative study, to interview the participants after their participation in the ACT treatment. This would give my project a more holistic approach. While delivering the treatment I got to know the participants better and I would really like to have more time to formally record their views on the treatment they received. However, this additional work

would have required an additional researcher's time, as I was involved in delivering the intervention, and conducting the exit interviews myself would introduce researcher bias.

6.10 Overall Conclusions

This thesis successfully addressed and provided evidence for the possibility of applying the PF model and ACT treatment to people with PDN in the UK. Three studies were conducted with the following conclusions drawn:

- Depression, anxiety, poor sleep and low quality of life are positively associated with pain outcomes in PDN. The evidence of the existing research is of moderate quality.

- PF may be relevant in the context of PDN. However, pain intensity appears more salient and more research is required to investigate these factors.

- The results of this thesis must be treated with caution due to the limitations described. However, online ACT only appears to be acceptable to a minority of participants with PDN. Among those willing to complete it, they may achieve some benefit to their wellbeing and functioning.

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Appendices

Appendix A: Systematic Review Protocol (PROSPERO)

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

Psychosocial factors in painful diabetic neuropathy: a systematic review of treatment outcome and survey studies

Kitty Kioskli, Whitney Scott, Stavros Kylakos, Kirsty Winkley, Lance McCracken

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Review question

Which are the existing psychological interventions for people with painful diabetic neuropathy (PDN)?
Which modifiable psychosocial factors are associated with PDN?
Which are the important clinical outcomes in relation to PDN?
What is the methodological quality of the existing studies?

Searches

The following online databases will be searched: MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, Web of Science and PsycINFO. References lists will be searched, by hand, for additional eligible studies. Additionally, Conference Proceedings Citation Index, through Web of Science, will be searched to identify any relevant conference proceedings and trials registries (e.g. ISRCTN, ClinicalTrials.gov).

Types of study to be included

The search will have no restriction on date of publication. The included studies will be any published study involving psychological treatments, intended to impact on physical functioning, emotional functioning (i.e. depression, stress, anxiety), pain experience, pain-related interference, symptoms and adverse effects (i.e. diabetes complications) and/or quality of life in patients with PDN. Also, included will be any studies designed to investigate relations between psychological factors (meaning emotions, thoughts or cognitive characteristics that affect a person's behaviour, attitude and functions, and can influence their way of thinking and decision making) and these same outcomes, such as retrospective or prospective survey studies.
Exclusion: Studies will be excluded if not written in English.

Condition or domain being studied

Painful diabetic neuropathy.

Participants/population

Inclusion:
1)Adult human subjects (>=18 years at the time of their entry into the study).
2)The sample of patients should have a clear diagnosis of PDN.
Exclusion:
1)Neuropathic pain of other causes.
2)Educational interventions.

Intervention(s), exposure(s)

1) Any psychological treatment aimed at addressing psychological factors deemed to be important in the functioning and well-being of people with PDN.
2) Studies measuring psychosocial factors for PDN and allowing examination of these in relation to clinical outcomes, particularly if these are modifiable.

Comparator(s)/control

All comparators are eligible for this systematic review.

Context

Diabetes mellitus (DM) is a common endocrine disorder, often significantly impacting on quality of life. The incidence of DM is increasing due to factors such as obesity, poor physical activity and an ageing population. PDN is one complication that rises from diabetes, mainly caused by pathological microvascular changes to the small nerve fibres, especially at the feet and hands. PDN has a great impact on both the individual (i.e. on distress and functioning) and society (i.e. on employment and healthcare costs). PDN is usually managed with medication. The existing literature reveals that pharmacological treatments have limited effectiveness and patients remain in pain and distress. There are very few reviews of psychological interventions for neuropathic pain, such as diabetic neuropathy, but existing evidence appears to show that psychological treatments are effective for people with chronic pain in general. However, the potential efficacy of the treatments, as applied to PDN, is unclear, suggesting the need for further research on this topic. The present study will expand and update previous related reviews of the current literature (e.g. Davies et al., 2015), again with a focus on the role of psychological factors and the effectiveness of existing psychological interventions. The aim of this review is to guide the design of a new practical and effective approach to treatment, if possible.

Primary outcome(s)

The collected primary outcomes will fall in, at least one, of the following domains:
1) Physical functioning.
2) Emotional functioning (i.e. depression, stress, anxiety).
3) Pain experience.
4) Pain related interference.
4) Symptoms and adverse effects (i.e. diabetes complications).
5) Quality of life.

Secondary outcome(s)

None

Data extraction (selection and coding)

Two independent reviewers (Miss Kioskli and Mr Kylakos), will run the searches on the selected electronic databases, to:
1) Review titles and abstracts for eligibility; papers not relevant to the study and duplicates will be removed.
2) Review and analyse the full texts (of the short-listed studies).
The inclusion and exclusion criteria of the studies will be applied by the same reviewers, and discussed to reach a consensus, where required. If any disagreements cannot be resolved through discussion, a third reviewer (a member of the supervisory team) will resolve the disagreement.
Data extraction will include the following: studies' bibliographic details (i.e. publication date, number of authors, country, journal), number and names of searched databases, types of studies (i.e. RCT), types of interventions, psychosocial factors, outcomes characteristics (i.e. pain-related), patients' and setting description, description of the condition and the diagnostic tools. The data will be extracted from the eligible studies, by the two reviewers. If the reviewers fail to reach a consensus, again, a third one will resolve any disagreements.

Risk of bias (quality) assessment

The quality assessment of the present study will be done through Downs and Black, (1998) quality assessment tool. This tool has been identified as appropriate for the quality assessment in systematic reviews. It is applicable to both randomised and non-randomised trials and other observational studies. The checklist will be modified minimally to meet the needs of the current systematic review, as is often done. The checklist will be administered to two independent reviewers (APK and SK) and will also be cross checked for consistency. Any disagreements will be resolved by a third reviewer.

Strategy for data synthesis
Narrative synthesis according to established guidelines by Popay et al., 2006, will be performed to summarise the collected data. Additionally, meta-analysis will be performed where a sufficient number of studies report associations between the same outcome category and psychosocial factors.

Analysis of subgroups or subsets
Not applicable.

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Conflicts of interest
None known

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Country
England

Stage of review
Review_Completed_not_published

Subject index terms status
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Subject index terms
Humans; Neuralgia; Surveys and Questionnaires; Treatment Outcome

Date of registration in PROSPERO
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Date of publication of this version

20 December 2017

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Versions

27 March 2017
27 May 2017
28 June 2017
13 September 2017
20 December 2017

Appendix B: Systematic Review Quality Assessment Tool for Observational Studies (Downs & Black, 1998)

Modified Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies

Reviewer's initials _____
First Author _____ *Journal:* _____ *Year published*_____

Reporting		Yes	No	U/D	*Partially*
1.	Is the hypothesis/aim/objective of the study clearly described?	1	0	0	
2A.	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	0	0	
2B.	Is the cardiometabolic disease biomarker of interest a primary outcome?	1	0	0	
3.	Are the characteristics of the study population included in the study clearly described?	1	0	0	
4.	Are the interventions under study clearly described?	2	0	0	1
5.	Are the distributions of principal confounders in each group of study participants to be compared clearly described?	1	0	0	
6.	Are the main findings of the study clearly described?	1	0	0	
7.	Does the study provide estimates of the random variability (e.g., standard error, standard deviation, confidence intervals, interquartile range) in the data for the main outcomes?	1	0	0	
8A.	Have all important adverse events/negative outcomes that may be a consequence of the intervention been reported?	1	0	0	
8B.	Were the screening criteria for study eligibility specified?	1	0	0	
9.	Have the characteristics of study participants lost to follow up been described?	1	0	0	
10.	Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1	0	0	

Total reporting score:_____ /13

External validity		Yes	No	U/D	*Partially*
11.	Were the study participants asked to participate representative of the entire population from which they were recruited?	1	0	0	
12.	Were study participants who agreed to participate representative of the entire population from which they were recruited?	1	0	0	
13.	Were the staff, places, and facilities where the study participants received the intervention representative of the intervention the majority of subjects receive?	1	0	0	

Total external validity score:_____ /3

Internal validity – bias		Yes	No	U/D	*Partially*
14.	Was an attempt made to blind study participants to the intervention they received?	1	0	0	
15.	Was an attempt made to blind those measuring the main outcomes of the intervention?	1	0	0	
16.	If any of the results of the study were based on "data dredging," was this made clear?	1	0	0	
17.	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of study participants, or in	1	0	0	

	case-control studies, is the time period between the intervention and outcome the same for cases and controls?				
18.	Were the statistical tests used to assess the main outcomes appropriate?	1	0	0	
19.	Was compliance with the intervention reliable?	1	0	0	
20.	Were the main outcome measures used accurate (valid and reliable)?	2	0	0	1

***Total bias score*:_____ /8**

Internal validity – confounding		Yes	No	U/D	*Partially*
21.	Were the study participants in the different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	1	0	0	
22.	Were study participants in the different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1	0	0	
23.	Were study participants randomized to intervention groups?	2	0	0	1
24.	Was the randomized intervention assignment concealed from both study participants and intervention staff until recruitment was complete and irrecoverable?	1	0	0	
25.	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	1	0	0	
26.	Were losses of study participants to follow-up taken into account?	1	0	0	

***Total confounding score*:_____ /7**

Power		Yes, ≥2 outcome	Yes, 1 outcome	No
27.	Did the study mention having conducted a power analysis to determine the sample size needed to detect a significant difference in effect size for one or more outcome measures?	2	1	0

***Total power score*:_____ /2**

****Total quality score: _____ /33***

*Note. *sum of all domain scores*

Appendix C: Systematic Review Quality Assessment Tool for RCTs (Higgins, 2011)

Study details

Reference	

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: | Comparator:

Specify which outcome is being assessed for risk of bias	
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	

Is the review team's aim for this result…?

- ☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

☐ Journal article(s) with results of the trial

☐ Trial protocol

☐ Statistical analysis plan (SAP)

☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)

☐ "Grey literature" (e.g. unpublished thesis)

☐ Conference abstract(s) about the trial

☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)

☐ Research ethics application

☐ Grant database summary (e.g. NIH Reporter or Research Councils UK Gateway to Research)

☐ Personal communication with trialist

☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?		Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA / Y / PY / PN / N / NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY / PN / N / NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		Y / PY / PN / N / NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / PN / N / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias		
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Appendix D: Systematic Review Data Extraction Form

Reviewer Name	
Authors	
Publication Year	
Journal	
Publication Type	Full text peer-reviewed article: Published Thesis:

Study Details	Description as stated in paper	Location in text (page and paragraph # or section #)
Study Design	Cross-sectional: Prospective cohort: Case-control: Observational: Other:	
Geographic Location of Study		
Recruitment Sites (i.e. hospital, charity) and methods (i.e. poster advertisements)	<u>Describe recruitment method:</u>	
Inclusion/Exclusion Criteria		
Sample Size (if case-control or group comparison, report *n* for pain and pain-free groups)		
Age (mean, SD, & range) (if case-control or group comparison, report this for each		
Sex: (if case-control or group comparison, report this for each group)	% Female: %Male:	
Race/Ethnicity (if case-control, report this for each group, if reported)		

Time since PDN Diagnosis (mean & SD; or median & range) (if case-control or group comparison, report this for each group, if reported)		
Taking Pharmacological Medication (if case-control or group comparison, report this for each group, if reported)	%Yes	
Medication Type (list type and % of participants taking that type) (if case-control or group comparison, report this for each group, if reported)		
Co-morbidities List type and frequency (%) (if case-control or group comparison, report this for each group, if reported)		
How was presence of neuropathy defined by the authors?		
PDN Duration (mean & SD; or median & range)		
Pain Assessment: list measures used and aspects of pain/functioning/QoL that were measured) *i.e.: BPI (pain intensity and interference); EQ-5DL (quality of life)* Note: If multiple items of pain intensity are assessed and presented separately in the analyses (e.g., present, average, least, worst), extract data only from the average pain intensity; if average is not reported, extract worse pain intensity)		
Psychosocial Variable(s) assessed (list all)		
Psychosocial Assessment: list measures used and psychosocial aspects *i.e.: PHQ-9 (depression symptoms)*		
Effect Size (mean): *Note: Some relevant measures of association/ effect sizes: Pearson's r correlation (i.e., for correlational studies looking at association between pain and a psych variable); Within a multivariate regression model, the measure of association would be Beta and RSquared change and their tests of significance.* *Odds Ratios (unadjusted or adjusted) predicting a dichotomous outcome (e.g., a psych variable predicting the presence of PN or no PN); Also, tables with frequencies (also called 'event data') and chi-square analyses—for example, a table with the number of depressed people in the PN group versus the number of depressed people in the no PN group.*		

Tables might also report the means and SD of continuous variables for a between groups comparison (i.e. they might compare the severity of depression symptoms between the PN and no PN groups). Here, extracting the mean and SD for each group, along with the t-test or ANOVA value is useful.		

Appendix E: Systematic Review Supplementary Material for Published Paper in Chapter 3

TableS1: Sample Search Strategy (EMBASE)

Painful Diabetic Neuropathy search terms

1. Painful Diabetic Neuropath*

2. Diabetic Neuropath*

3. Painful Diabetic Polyneuropath*

4. Diabetic Polyneuropath*

5. Diabetic neuropath* pain

6. Diabetes

7. Peripheral Nervous System Diseas*

8. Peripheral Nervous System Disorder*

9. Painful Diabetic Peripheral Neuropath*

10. Diabetic Autonomic Neuropath*

11. ((neuropathic or nerve*) adj3 pain*).tw.

12. (Neuropath* or Polyneuropath*).tw.

13. sensory neuropath*

14. OR/1-13

Psychological Interventions search terms

15. exp psychotherapy/

16. behavior therapy/ or cognitive therapy/

17. exp Biofeedback, Psychology/

18. behavio#r therap*.tw.

19. cognitive therap*.tw.

20. (relax* adj3 technique*).tw.

21. (relax* adj3 (technique* or therap*)).tw.

22. meditat*.tw.

23. psychotherap*.tw.

24. (psychological adj2 (treatment* or therap* or intervention*)).tw.

25. group therapy.tw.

26. self-regulation training.tw.

27. coping skill*.tw.

28. pain-related thought*.tw.

29. (behavio#r* adj3 rehabilitat*).tw.

30. (mind and body relaxation technique* or mind-body relaxation technique*).tw.

31. exp mind-body therapies/ or relaxation therapy/

32. Mindfulness.tw.

33. (Mindfulness-based stress reduction or MBSR).tw.

34. (Mindfulness-based cognitive therapy or MBCT).tw.

35. (Acceptance-based or acceptance based).tw.

36. (Acceptance and commitment therap* or Acceptance and commitment intervention* or Acceptance and commitment treatment*).tw.

37. Or/ 15-36

Psychosocial search terms

38. Psycholog$.mp

39. Psychosocial factors/

40. Psychological factors.mp

41. Adjustment.mp

42. Depression.mp

43. Anxiety.mp

44. exp mood/

45. exp Social adjustment/

46. Social function$.mp

47. exp Quality of Life/

48. Coping.mp

49. Belief$.mp

50. Cognition.mp

51. Perception.mp

52. Fear avoidance.mp

53. Interference.mp

54. Catastrophi?ing.mp

55. Acceptance.mp

56. Willingness.mp

57. Mindfulness.mp

58. Endurance.mp

59. Biopsychosocial

60. Or/ 38-59

Combined Search

→Limit to humans 1981-Current

14 AND 37 OR 60

TableS2: Psychosocial variables and pain outcomes

Study	Diagnosis of PDN	Neuropathy (Assessment)	Pain Variables (Assessment)	Psychosocial Variables (Assessment)	Summary of Main Findings
AL-Mahmood et al. (2018)	Subjective & objective measurement of PDN symptoms, reported	DN4	-	QOL (ADDQOL)	27.8% of participants reported the negative impact of diabetes on their QOL, and 37.8% reported the belief that their QOL would have been higher if they were not diagnosed with diabetes.
Benbow et al. (1998)	Subjective measurement of PDN symptoms, reported	MPQ	Pain Severity (VAS)	QOL (NHP)	Patients with neuropathy had higher scores in 5/6 NHP domains (showing impaired QOL) compared to diabetic patients with no pain ($p<0.01$) and the non-diabetic group ($p<0.001$).
Bouhassira et al. (2013)	Subjective & objective measurement of PDN symptoms, reported	DN4, MNSI, 10-g-Semmes-Weinstein	-	QOL, sleep, depression, anxiety (MOS SF-12, SF-36, MOS, HADS)	Prevalence of chronic neuropathic pain was 20.3% [95% CI 17.4–23.1]. MNSI revealed that pain was related to polyneuropathy in 80.1% of these participants. Patients with pain had a poorer quality of life, reduced sleep quality, and anxiety and depression were more present compare to patients without pain. Neuropathic characteristics acted as predictors for these impairments.
Currie et al. (2006)	Subjective & objective measurement of PDN symptoms, reported	Physician's diagnosis, NTSS-6-SA	-	QOL (EQ-5D, SF-36, QoL-DN)	For patients with a clinically confirmed diagnosis of DPN, the mean NTSS-6-SA score was 6.16 vs 3.19 in patients without DPN ($p<0.001$). All quality of life measures showed a deterioration between these groups: the SF36 general health profile fell from 59.9 to 25.5 ($p<0.001$) and the QoL-DN increased from 25.8 to 48.1 ($p<0.001$).

Dobrota et al. (2014)	Subjective & objective measurement of PDN symptoms, reported	LANSS, EFNS, NE	Presence of pain (VAS)	QOL, depression, sleep (SF-36, BDI)	The most significant differences between the groups were in sleeping disorders, impaired QOL, problems regarding defecation and micturition and medication which were more expressed in PDPN subjects than the patients without painful DPN.
Galer et al. (2000)	Subjective measurement of PDN symptoms, reported	NPS	Pain Interference (mBPI)	QOL (mBPI)	Participants reported major interference of pain in sleep and enjoyment of life resulting to a substantial impact on QOL.
Geelen et al. (2016;2017	Subjective measurement of PDN symptoms, reported	Duration of complaints for neuropathic pain	Pain Intensity/Disability (VAS, PDI)	Fears, QOL (QOL-DN, HFS, PASS-20, TSK, TSF, FES-I, BFNE)	Fears were independently associated with QOL-DN and PDI ($p < 0.001$). Pain intensity, duration and FES-I were strongly associated with QOL-DN ($R2 = 0.603$). Pain intensity, gender (male) and FES-I were also strongly associated with PDI ($R2 = 0.526$).
Gore et al. (2005; 2006)	Subjective & objective measurement of PDN symptoms, reported	Physician's diagnosis, BPI-PDN	-	Sleep, anxiety, depression, QOL (MOS, HADS, SF-12v2)	Average and worst pain scores (BPI-DPN) were 5.0 + 2.5 and 5.6 + 2.8. 71.4% reported moderate-to-severe average and 75.3% reported worst pain intensity.
Hoffman et al. (2009)	Subjective measurement of PDN symptoms, reported	MPQ	Pain Severity/Interference (mBPI-sf, VAS)	QOL, anxiety, depression, sleep (MOS, HADS, EQ-5D UK Index, EQ-5D Japan Index)	Subjects reported at least moderate levels of pain severity. Mean + SD scores for average pain: Asia 5.9 + 1.8, Latin America 6.7 + 1.6, Middle East 6.6 + 1.7. Mean + SD scores for mBPI-sf: Asia 4.7+2.3, Latin America 5.6+2., Middle East 5.5+2.3. All subjects reported difficulties with sleep, health and functioning, sleep resulting in increasing pain severity.
Jacovides et al. (2014)	Subjective & objective measurement of PDN symptoms, reported	DN4	-	Sleep, QOL (DSIS, EQ-5D)	Prevalence of DPNP was 30.3%. EQ-5D scores (mean, +SD) were 0.84 + 0.16 for subjects without DPNP and 0.64 + 0.25 for subjects with DPNP. DSIS scores (mean + SD) were 0.83 +1.90 for subjects without DPNP and 3.62 + 2.96 for subjects with DPNP.

Kulkantrakorn et al. (2013)	Subjective & objective measurement of PDN symptoms, reported	NPS, DN4, SF-MPQ	Pain Severity (VAS)	QOL (SF-36)	In NPS, sharp pain was the most common reported symptom while itching the lesser one. VAS had a mean of 53mm. SF-36 showed that physical functioning was the most affected domain while social functioning the least.
Levterova et al. (2018)	Subjective & objective measurement of PDN symptoms, reported	DN4	-	QOL (SF-36)	Overall, the prevalence of DPN was 43% among all participants. DPN with pain was 14% among all participants with DPN. Participants with DPN with pain (group 1) had statistically lower QOL compared to participants with DPN without pain (group 2).
Lewko et al. (2007)	Subjective measurement of PDN symptoms, reported	Self-reports	-	Acceptance of illness, QOL (AIS, HRQOL, SF-36)	QOL was significantly reduced in subjects with PDN and also was related to the levels of illness acceptance. Factors influencing illness were feelings of being a burden ($p \leq 0.05$) and the belief that people around them are becoming anxious by their illness ($p \leq 0.05$)
Mai et al. (2015)	Subjective & objective measurement of PDN symptoms, reported	DN4, clinical criteria	Pain Intensity/Severity /Presence (BPI, PDI)	QOL, mood, catastrophizing, satisfaction (SF-12, POMS, PCS, PGS)	At 12-month follow-up, 37.2% of patients achieved pain reduction of ≥30%, 51.2% of patients achieved functional improvement of ≥1 on the BPI and 30.2% of patients achieved both pain reduction and functional improvement.
Otis et al. (2013)	Subjective measurement of PDN symptoms, reported	Self-reports	Pain Interference/Severity (WHYMPI)	Depressive symptoms (BDI)	The CBT group showed decreases in pain severity (B = -0.54) and pain interference (B = -0.77) from pre-treatment to 4-month follow-up. No significant differences were shown on the control group on pain severity (B = 0.00) and pain interference (B = -0.09). Depressive symptoms did not change for any group.
Pfamatter (2012)	Subjective & objective measurement of PDN symptoms, reported	Physician's diagnosis, DNSS	Pain Severity (MPI)	Control of pain (SOPA)	No significant associations were produced. The effect sizes suggest that the experimental group experienced less pain and decrease in temperature within the sessions.

Sadosky et al. (2013)	Objective measurement of PDN symptoms, reported	Physician's diagnosis	Pain Severity/Intensity /Functioning (BPI-SF)	QOL (SF-12v2, EQ-5D-3, MOS, HADS, WPAI-SHP)	The pain severity score was 5.2 (mean), and 79.5% of the participants reported moderate or severe pain. Overall, the function and pain interference scores were 5.0 (mean) overall. The mean overall activity impairment across all participants was 52.3%. Participants with severe pain had worse pain interference with sleep, function and health status (P<0.0020).
Selvarajah et al. (2014)	Subjective & objective measurement of PDN symptoms, reported	NDS, NPS	-	QOL, catastrophizing, acceptance, anxiety, depression (QOL-DN, CPA-Q, PCS, HADS)	Overall, the prevalence of emotional distress was 51.4%. Catastrophic thinking, pain-related restriction of QOL, age, marital status and employment acted as independent contributors to increase symptoms of anxiety and depression.
Teixeira (2010)	Subjective measurement of PDN symptoms, reported	NPS	-	QOL, sleep, mindfulness (NeuroQol, PSQI)	The results suggested no significant statistical difference between the intervention and control group.
Themistocleous et al. (2016)	Subjective & objective measurement of PDN symptoms, reported	PainDETECT, DFNS, IENFD, NCT, NE, TCSS, NPSI, DN4	Pain Interference (BPI)	QOL, pain catastrophizing, depression, anxiety, insomnia (SF-36, PCS, PASS, DAPOS, ISI)	Participants with PDPN scored higher on DN4 and painDETECT and correlated well with the mean score obtained from the 7-day pain intensity diary. Participants with moderate/severe PDNP scored higher on PCS, DAPOS, PASS-20, ISI, BPI and SF-36. Hence, these participants had poorer quality of life.
Tölle et al. (2006)	Subjective & objective measurement of PDN symptoms, reported	Self-reports, physician's diagnosis	Presence of pain (mBPI-SF)	QOL (EQ-5D)	Pain severity was strongly associated with greater pain interference scores (P<0.001).

Van Acker et al. (2009) [44]	Subjective & objective measurement of PDN symptoms, reported	Neuropen, DN4	Pain Intensity (VAS)	QOL (SF-12)	The prevalence of DPN was 43% (95% CI 40.1–45.9). The prevalence of DPN-P was 14% (95% CI 12.1–16.2). Nephropathy, obesity, low HDL cholesterol and high triglyceride levels were independently associated with DPN and/or DPN-P. Physical and mental components of QoL were significantly altered by DPN-P. Only half of the DPN-P patients were using analgesic treatment, while 28% were using anticonvulsants or antidepressants.
Vileikyte et al. (2005)	Subjective & objective measurement of PDN symptoms, reported	NDS, VPT, NeuroQol	-	Depressive symptoms (HADS, IPQ-R)	NDS and VPT were strongly associated with HADS. The relationship between foot ulceration and depression was non-significant.
Vileikyte et al. (2009)	Subjective & objective measurement of PDN symptoms, reported	NDS, VPT, NeuroQol	-	Depressive symptoms (HADS, IPQ-R)	NDS at baseline predicted increased HADS-D over 18 months. Increased pain, unsteadiness and ADL restrictions from baseline to 9 months predicted increased HADS-D over 18 months. Change in social self-perception from baseline to 9 months predicted increased HADS-D.
Wickramasinghe et al. (2016)	Subjective & objective measurement of PDN symptoms, reported	DN4	-	QOL (NeuroQoL)	74% of the participants suffered from DPN while 97.1% were asymptomatic. 40% of the patients with diagnosed DPN reported that they have a poor quality of life. 74% mentioned that their symptoms reduced with pharmacological treatment.
Zelman et al. (2005)	Subjective & objective measurement of PDN symptoms, reported	BPI-PDN, physician's diagnosis	Pain Severity (VRS)	QOL (EQ-5D, SF-12v2)	Mean BPI-DPN Interference was 2.1 (SD=2.1) for mild pain, 4.9 (SD=1.9) for moderate pain and 7.4 (SD=1.6) for severe pain. These categories of DPN pain severity are based on interference with daily function.
Zelman et al. (2006)	Subjective measurement of PDN symptoms, reported	BPI-PDN	-	Sleep, Anxiety (MOS, HADS)	Individuals with painful DPN reported impaired sleep compared to postherpetic neuralgia patients, the general population, and the chronic disease sample.

Note: "-": not reported, ADDQOL: Audit of Diabetes-Dependent Quality Of Life, AIS: Acceptance of Illness Scale, BDI: Beck Depression Inventory, BFNE: Brief Fear of Negative Evaluation Scale, CPA-Q: Chronic Pain Acceptance Questionnaire, CPPN: Chronic Painful Peripheral Neuropathy, DAPOS: The Depression Anxiety and Positive Outlook Instrument, DFNS: German research network of neuropathic pain, DN4: Douleur Neuropathique 4, DNSS: Diabetic Neuropathy Symptom Score, DPN: Diabetic Peripheral Neuropathy, DPNP: Diabetic Peripheral Neuropathic Pain, DSIS: Daily Sleep Interference Scale, EFNS: European Federation of Neurological Societies, EQ-5D: EuroQol, FES-I: Falls Efficacy Scale-International, FS: rating scale for current feelings, HADS: Hospital Anxiety and Depression scale, HFS: Hypoglycaemia Fear Survey, IENFD: Intraepidermal Nerve Fibre Density, IPQ: Illness Perceptions Questionnaire, ISI: Insomnia Severity Index, LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, mBPI: modified Brief Pain Inventory, MNSI: Michigan Neuropathy Screening Instrument, MOS: Medical Outcomes Study-sleep scale, MOS SF –12: Medical Outcomes Short Form 12 scale, MPI: Multidimensional Pain Inventory, MPQ: McGill Pain Questionnaire, NCT: Nerve Conduction Tests, NDS: Neuropathy Disability Score, NE: Neurological Examination, NeuroQol: Neuropathy and Foot Ulcer-specific Quality of Life Instrument, NHP: Nottingham Health Profile, NPS: Neuropathic Pain Scale, NPSI: The Neuropathic Pain Symptom Inventory, NRS: Numeric Rating Scale, NSS: Neuropathy Symptom Score, NTSS-6-SA: Neuropathic Total Symptom Score Self-Administered, PASS-20: Pain Anxiety Symptom Scale, PCS: Pain Catastrophizing Scale, PDI: Pain Disability Index, PDPN: Painful Diabetic Polyneuropathy, PGS: Patient Global Satisfaction, POMS: Profile of Mood State, PPIS: Present Pain Intensity Scale, PSMPI: Pain Severity scale of the Multidimensional Pain Inventory, PSS: Pain Symptom Score, PSQI: Pittsburgh Sleep Quality Index, QOL: Quality of Life, QOL-DN: Norfolk Quality of Life Questionnaire, SF-MPQ: Short Form, SF-12: Short Form Health Survey, SF-36: Short Form Health Survey, SOPA: Survey Of Pain Attitudes, TCSS: Toronto Clinical Scoring System, TSF: Tampa Scale of Fear of Fatigue, TSK: Tampa Scale of Kinesiophobia, VAS: Visual Analogue Scale, VPT: Vibration Perception Threshold, VRS: Verbal rating scale, WPAI-SHP: Work Productivity and Activity Impairment-Specific Health Problem, WHYMPI: West Haven Yale Multidimensional Pain Inventory

Appendix F: Survey's and Feasibility's Study Protocol

Institute of Psychiatry, Psychology & Neuroscience

KING'S College LONDON

Title: The Development of Contextual Cognitive Behavioural Approach to PDN

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Background

The Problem of Chronic Neuropathic Pain

Chronic neuropathic pain (CNP) is the type of pain caused by a nerve injury or disease and is considered as a serious issue in the UK. There are several causes for CNP such as, pain arising in stroke, spinal cord injury, multiple sclerosis, post-surgical pain, diabetic neuropathy, post herpetic neuralgia, and facial neuralgias, among other conditions. According to Haanpäa et al, (2011), 3.3% to 8.2% of the general population suffers for CNP due to various causes. As a result, this condition involves great suffering and disability for the individuals, while the health-care system is significantly burdened (Jensen et al., 2007).

Most interventions for CNP are pharmacological, including medications such as tricyclic antidepressants (TCAs), anticonvulsants, and opioids. However, a recent systematic review of 174 randomized controlled clinical trials (RCTs) of pharmacological treatment for neuropathic pain, frankly, yielded disappointing results (Finnerup, Sindrup, & Jensen, 2010). There has been a substantial increase in the number and quality of trials conducted in the past five years but overall little improvement in efficacy. For example, some of the most effective drugs are those in the class of TCAs. The number needed to treat (NNT) to achieve at least 50% pain relief, ranges from 2.1 for painful polyneuropathy to 2.8 for post herpetic neuralgia. On the other hand, the number needed to harm (NNH), that is the number of patients treated for one to drop out due to adverse effects, is 15.9. The next best front-line drug, pregabalin, has an NNT ranging between 3.8 for mixed neuropathic pain to 5.6 for central neuropathic pain (Finnerup et al., 2010). Conclusively, as implied by Finnerup et al, (2010), even though pharmacological interventions are considered the most effective therapeutic option for patients who suffer from CNP, patients still experience great pain after receiving the medication.

Psychological Treatment Methods

Psychological treatment methods, particularly those based on Cognitive Behavioral Therapy (CBT) represent a viable alternative or addition for the treatment of chronic neuropathic pain. Broadly considered CBT interventions, are regarded as the most effective and cost-effective methods for treating chronic pain when compared to a range of pharmacological, surgical, and interventional procedures (Gatchel & Okifuji, 2006). There are now more than five systematic reviews that support the effectiveness of CBT for chronic pain (Eccleston et al., 2009; Guzmán et al., 2001; Morley et al., 1999). These approaches are not only able to reduce pain, but, importantly, also to improve daily activities, emotional functioning, work status, and to reduce healthcare costs (Gatchel & Okifuji, 2006). However, CBT interventions are rarely applied to patients suffering from CNP. In particular, there is only one RCT, by Otis et al, (2013), that applied CBT to Painful Diabetic Neuropathy (PDN) patients, yielding promising results suggesting that CBT could improve patients' skills to experience less pain and be more physically active.

Some researchers have suggested that different types of pain may require different psychological interventions. However, there is little evidence to support this. The literature reveals that, individuals who suffer from either chronic pain or neuropathic pain experience major impact in most aspects of their life including mood, mobility, work, sleep, and overall quality and enjoyment of life (Jensen et al., 2007; Schmader, 2002). One may conclude that, the impact of pain appears the same regardless of the different patient groups.

Studies that compared patients with neuropathic pain to patients with non-neuropathic pain in terms of psychological variables, have found the groups to be much more similar, rather than different. In a cross-sectional study comparing people with post-herpetic neuralgia versus low back pain there were no significant differences in self-reported measures of pain, mood, fear, or pain acceptance (Daniel et al., 2008). Similar findings were shown in a study comparing patients with

neuropathic (trigeminal neuralgia) and non-neuropathic (temporomandibular disorder) orofacial pain. Once again, the groups were not different on measures of depression, anxiety, catastrophizing, or physical and social functioning, even though they differed in some of their reported sensory aspects of their pain (Gustin et al., 2011). Another study showed group differences between patients with fibromyalgia and patients with peripheral neuropathic pain, however, the groups were small and were confounded by the recruitment methods used, and by gender (Gormsen et al., 2010).

There have been few studies of psychological treatments for neuropathic pain. A recent systematic review identified 14 studies which involved adults with neuropathic pain and cognitive or behavioural interventions (Van de Wetering et al., 2010). Only three of these studies were RCTs and only one was regarded as having good methodological quality. Upon further inspection, however, this trial included patients diagnosed with "long-term non-specific spinal pain" and not neuropathic pain as such (Jensen et al., 2001). Hence, it was included in the systematic review erroneously. Another of the RCTs tested the effect of viewing an intact limb in a mirror on phantom limb pain, referred to it as "viewing a virtual limb" (Brodie et al., 2007), a method that is not regarded as a standard cognitive or behavioural method. The final RCT was a feasibility and acceptability study of CBT for HIV-related neuropathic pain (Evans et al., 2003). In this study, the CBT group showed significantly greater reductions than the control group in depression and general emotional distress, however, there was a 57% dropout rate in the CBT group. Hence, the treatment was regarded as having limited feasibility and acceptability in this group. Other treatments included in the systematic review included "healing touch," reflexology," and a method called "image imprinting" to address body image, none of which would be recognised as a standard method within CBT. All the above reveal that, the evidence for cognitive and behavioural approaches to neuropathic pain is limited and further studies are needed to determine efficacy of psychological interventions in this population (Van de Wetering, 2010).

Acceptance and Commitment Therapy

A relatively new and promising approach to chronic pain, within the wider range of cognitive and behavioural approaches, is Acceptance and Commitment Therapy (ACT) (Hayes et al., 1999, McCracken, 2005). ACT is a form of CBT that focuses specifically on increasing psychological flexibility. Psychological flexibility is the capacity to change or continue with behaviour, depending on which is more effective, according to one's goals and what the current situation affords. Psychological flexibility in turn includes processes of acceptance, values-based action, and other processes related to mindfulness. There are now at least four RCTs that support the efficacy of ACT as an approach for chronic pain in general (Dahl et al., 2004; Thorsell et al., 2011; Wetherell et al., 2011; Wicksell et al., 2008). One of these shows that ACT is at least as effective as traditional CBT for chronic pain and may be preferred by patients (Wetherell et al., 2011). There are also a number of larger scale effectiveness studies showing that ACT (a) is deliverable in NHS practice settings (McCracken et al., 2005; Vowles & McCracken, 2008), (b) is associated with a wide range of improvements in emotional, physical, and social functioning and reduced healthcare use (McCracken et al., 2005; Vowles & McCracken, 2008), (c) produces good long term results, such as at three years post treatment (Vowles et al., 2011) and, (d) appears to produce results specifically through changes in its theoretically proposed processes of change (McCracken & Gutiérrez-Martínez, 2011; Vowles & McCracken, 2010; Wicksell et al., 2010).

ACT is a highly flexible and variously scalable approach. It has been delivered in formats ranging from a self-directed workbook (Johnston et al., 2010), to four hours of individual treatment time delivered by a single treatment provider (Dahl et al., 2004), and up to 20 days of full time treatment in a group, residential, treatment environment, provided by an interdisciplinary team of treatment providers, specifically for highly complex problems of chronic pain (Vowles & McCracken, 2008). ACT has been deemed to have "strong research support" as a treatment for "general chronic pain" from

the American Psychological Association (Society for Clinical Psychology, 2011). None of the currently published trials has specifically focused on neuropathic pain.

Painful Diabetic Neuropathy

There are nearly 3 million people in the UK diagnosed with diabetes mellitus (DM) and this is expected to grow to 5 million by 2025 (Diabetes UK, 2011). One of the more common forms of neuropathic pain is associated with DM. Approximately 25% of all patients with DM develop painful diabetic neuropathy (PDN) and the prevalence of painful symptoms is up to 60% (Daousi et al., 2004; Davies et al., 2006, Mai et al., 2017). PDN, is considered a complex, multi-dimensional condition, possibly affecting the physical and mental health of the patient (Barrett et al., 2007). PDN, is usually described as a sense of burning, stabbing, aching and/or pricking mainly affecting areas like toes, legs, and feet and physically interfering with mobility, sleep, mood, and generally quality of life. Moreover, PDN despite the physical health it also affects the mental health of the patients by enhancing the levels of anxiety, catastrophizing thinking and depression (Geelen et al., 2016; Vileikyte et al., 2005) resulting in poorer outcomes, such as worsening pain-related disabilities (Gore et al., 2005). Although some patients may experience temporary symptoms' relief through interventions PDN is a chronic disease and a long-term suffering for most patients (Mai et al., 2017).

The summary presented here clearly highlights the importance of improving the health and well-being in patients with PDN by developing acceptable and potentially effective psychological interventions (Collins et al., 2009; Geelen et al., 2016; Vileikyte et al., 2005). This condition represents both a significant problem in its own right and a useful condition in which to test treatments that may offer wider benefits for neuropathic pain conditions in general. There are no published studies of ACT for PDN and the limited available evidence indicates that a CBT-based intervention like ACT has the potential to reduce pain in people with PDN.

People with PDN have clear treatment needs. While ACT may help them, little is known directly about the relevance of different components of ACT for this condition or about how to customize it for them. The proposed research will include two aims: (a) to preliminarily survey people with PDN on relevant treatment needs and then (b) to conduct a feasibility study of the resulting treatment design based on these.

Objectives

The overarching objective of this research is to assess the feasibility, acceptability, and potential efficacy of the ACT treatment, via the following objectives in Table 24:

Table 24: Research Objectives

Objective 1	Gather a more in-depth understanding of the patients' perspectives and beliefs associated to neuropathic pain
Objective 2	Examine the feasibility of such treatment by measuring recruitment and retention rates
Objective 3	Establish the best instruments for measuring variables by examining the quality, completeness, and variability of the data
Objective 4	Specify if ACT is as acceptable and credible approach for the participants
Objective 5	Determine whether the methods and procedures in treatment can be delivered effectively and with integrity

Research aims

This patient's survey and the feasibility study is a response to unmet treatment needs of people in the UK suffering from PDN, and to a particular lack of development of ACT-based approaches for these patients. Available evidence, limited as it is, suggests no reason to doubt the efficacy of broadly ACT-based approaches for CNP. Well controlled studies are needed to verify this reasonable presumption. There are also recent developments within ACT, that already have strong research support, offer flexible and highly efficient delivery options, and appear well-suited to the study population. PDN is being chosen as a condition on which to pursue this treatment development work, as the condition is relatively common, causes patients great problems, and overlaps with the areas of expertise represented in the research team.

Aims

- Assess the experience of pain from the perspective of PDN patients.
- Examine patients' treatment needs and preferences.
- Assess the suitability and feasibility of ACT as an acceptable and potentially effective intervention.
- Examine the feasibility and to pilot test a psychological treatment for PDN.
- Assess a feasibility of such a treatment by establishing recruitment and retention rates, the appropriateness and sensitivity of outcome measures, and acceptability to participants, through conducting a small feasibility study.

Hypothesis Being Tested

This research is not so much hypothesis driven as it is focused on a few key research questions. Through the methods described we will determine treatment needs and preferences, identify therapeutic priorities, develop these into a prototype treatment, and then test the feasibility of this, particularly in terms of deliverability and acceptability. In particular we will be able to specify the intervention's duration, techniques, processes emphasised, mode of delivery, and outcomes from phase one of this project and then test these aspects in phase two.

Study Design

The survey will adopt a cross-sectional design for patients who suffer from PDN and receive any type of treatment, pharmacological or psychological, or no treatment at all. This survey intends to include at least 200 participants with PDN, which will be recruited both online and face to face in order to achieve results that are likely to be reliable and the power to detect small correlations in the data.

The feasibility study will be an online single cohort, which will be linked to the survey. Based on this survey, the research team will develop an ACT-based intervention for PDN patients that can then be further tested for feasibility. The described feasibility study intends to include 30 patients suffering

from PDN. The total sample size is designed primarily to allow an efficient size to be conducted and to allow enough recruitment to observe retention rates.

Sample Size

For the survey, we used a regression-based a-prior estimation for required sample size based upon past data looking at cognitive and behavioural predictors in Multiple sclerosis. Modelling a regression equation with 12 predictors and an effect size of .15 (f^2=medium effect) with power set at .80, revealed an estimated require sample size of 127. We will aim to achieve a minimum sample size of 200 that will achieve the power needed and also provide enough sample size for secondary validity analyses of the instruments being used.

For the feasibility study, a sample size of approximately 30 participants would allow us to estimate the true population consent rate with a 11% margin of error (95% confidence level) for those meeting eligibility criteria. Past psychological research in patients with chronic pain, conducted by the team, suggest consent rates between 50-70%, assuming a more conservative uptake of 40%, and approximately 30% will meet both the inclusion and exclusion criteria. In line with recommended sample sizes of pilot feasibility trials (Billingham, Whitehead, & Julius, 2013; Browne, 1995; Viechtbauer et al., 2015) 30 patients is deemed sufficient to explore feasibility, acceptability, and potentially efficacy of the intervention, assuming retention rates of 80%, the true population consent rate will be with a margin of error of 14% (95% confidence interval). Achieving this sample size is considered feasible by the research team in the given timeframe.

Eligibility

The eligibility of the participants will be assessed through a screening pack which will include two self-report questions asking if they are adults and have confirmed diagnosis of diabetes and neuropathic pain and have the basic English reading ability and interest to participate.

Inclusion Criteria

Participants will have to fulfil the following criteria in order to take part to our research:

- Aged at least 18 years.
- Confirmed diagnosis of diabetes.
- Presence of painful diabetic neuropathy, for the last three months or more.
- Have full verbal and written proficiency in English.
- Willingness and ability to take part.
- Have computer literacy (where online procedures are involved).

Exclusion Criteria

Potential participants who are not able to understand verbal explanation or written information in English will regrettably be excluded. The measures are designed for self-administration and live translation would both undermine their validity and create unnecessary variability in the data. We do not have the resources or funding available produce and validate the standardised measures being used in other languages. We will monitor the number of potential participants excluded for this reason and if it is significant, we will use this information in planning future studies.

Recruitment

Potential participant will be approached both online and face to face.

Within the GSTT NHS site participants will be identified by the direct clinical care team. The research team will only approach the potential participant after the direct care team has obtained verbal consent for the research team to approach them about the study. The clinical care team will introduce the member of the research team to suitable potential participants. The member of the research team will explain the studies to potential participants in the waiting room of the relevant outpatient clinics and will answer any questions. The member of the research team will then provide the recruitment pack to potential participants. The recruitment pack will include: 1) Participant Information Sheet, 2) Consent Form and a, 3) Screening Questionnaire. All the recruitment materials are written in simple, easy to understand language, free of medical jargon. National Institute of Health Research (NIHR) guidelines have been followed when creating the Information Sheet and Consent Form. Participants will be encouraged to take at least 24 hours to consider their participation to the survey and discuss it with their family, GP, or the research team if they wish. It will be made clear that they may or may not be eligible to take part and their usual care will not be affected in any way. Also, participants can refuse to take part without giving a reason. Consent will be taken with the presence of a researcher either via Skype or face to face.

Participants will also be recruited online if necessary. The researcher will contact online organisations with an interest in the diabetes and related conditions to disseminate the present research. The questionnaires will be delivered online using Bristol Online Surveys (BOS) tool and the intervention will also be delivered online. BOS provides a protective privacy policy regarding e-mail addresses and personal information that is compliant with EU and international standards as specified in the Safe Harbor Framework regarding the collection, use and retention of personal

information. Responses will be anonymised at the point of data collection and no personal identifiers will be collected.

As the BOS tool is accessed via a hyperlink we will focus on organisations with an online presence, like Diabetes UK. The targeted organisations will be kindly asked to add a notice to their website, a message on their forums and send a message to their followers that highlights the study and provides the URL. Via the link participants will be provide with details about the studies before they begin. Initial questions will collect basic demographics information, for descriptive purposes, and a screening questionnaire will detect their eligibility for the study.

We anticipate that recruitment will take approximately 3 months. Also, participants will be kindly asked if they would also like to take part in further research, if yes, they will be asked to provide their contact details. Data will be analysed qualitatively in for some of the open-ended content and quantitatively, with SPSS, particularly for the numerical rating data and standardized measures. A flow chart summarizing the process explained can be found in Figure 18.

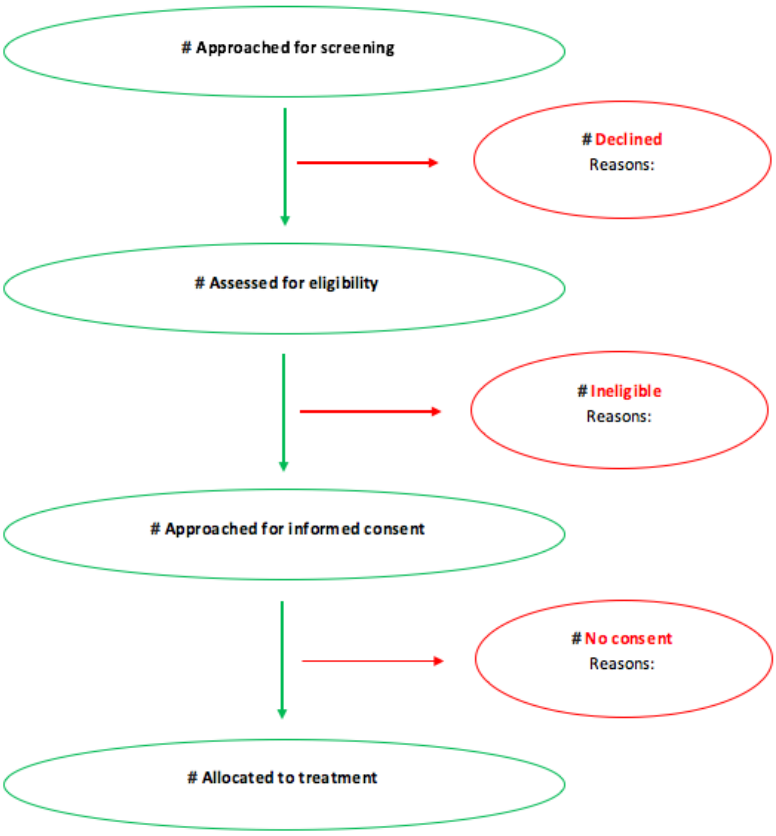

Figure 18: Anticipated flow of the participants

Assessment Instruments

The following questionnaires will be used in the present studies and consent will be obtained for all of them:

Demographic Questionnaire collecting the background information mentioned below: age, gender, ethnicity, pain history and pain location, level of education, occupation.

Screening pack, assessing participants' eligibility for the study: Self-report: Two questions asking the participants if they have a confirmed diagnosis of diabetes and neuropathy from their physician.

The following set of questionnaires, commonly used for chronic pain studies, will be included in this study. Standardized measures will include the following:

Pain Intensity scale: 0-10 numerical ratings of pain intensity. Participants will be asked to rate average pain in the past week on a 0-10 numerical scale.

Work and Social Adjustment Scale (WSAS): WSAS is a reliable self-report measure with great validity. It contains five-items which are rated to a 0-8 numerical scale (0=No impairment, 8=very severe impairment). WSAS assess "functional impairment" whith statements reffering to work, home management, social and private leisure, and relationships (Mundt, Marks, Shear, & Greist, 2002; Yu, McCracken & Norton, 2016).

Patient Health Questionnaire (PHQ-9): PHQ-9 is a reliable and validate measure for depressive symptoms, according to DSM-IV. It includes 9-items, and each item is rated on a four-point scale between 'not at all' and 'nearly every day' (Lowe et al, 2004; Kroenke et al, 2001).

Committed Action Questionnaire (CAQ-8): CAQ-8 intends to reveal the level of commitment participants have related to their goals, plans, activities and furthermore their psychological flexibility (McCracken, Chilcot & Norton 2015). Responses to the statements of the questionnaire will be rated to a 0-6 scale (0=Never True, 6=Always True).

The Chronic Pain Acceptance Questionnaire (CPAQ): CPAQ is a validate measure which reveals acceptance of pain through measuring: engagement in activity in the presence of pain, and willingness to experience pain without trying to control or avoid it (McCracken, 2010; McCracken, Vowles & Eccleston, 2004). CPAQ is a 20-item questionnaire, on a 6-point scale (0 = never true, 6 = always true). The higher score a participant reaches the greater acceptance of pain he/she have.

Self - Experiences Questionnaire (SEQ): The SEQ consists 29-items and aims to measure self-related process within the psychological flexibility model (Yu, McCracken & Norton, 2016). All items are rated on a 0–6 scale from "never true" to "always true".

The Cognitive Fusion Questionnaire (CFQ-7): The CFQ offers a psychometrically sound measure of cognitive fusion and consists of 7-items on a 7-point scale (1=never true, 7=always true). CFQ is considered very valuable for the researchers and clinicians who intend to assess psychological processes (Gillanders et al., 2014).

At the end, there will also be a questionnaire which will help the research team design and implement an acceptable and potentially effective ACT psychological treatment. The questionnaire will ask for the personal views of the participants regarding the treatment delivery format.

Treatment

The intervention is a tailored ACT-based self-management intervention which will be delivered online, unless results from the feasibility survey clearly suggest another format. The purpose of this intervention is to improve participant daily functioning via increased psychological flexibility. The intervention's outline can be found in Figure 19. The development of the PDN ACT-based intervention involved a multidisciplinary team of psychologists, health professionals and diabetes specialists.

The ACT treatment package will embrace the core treatment processes of acceptance, cognitive defusion, mindfulness, and values-based action. Methods will include practice in contacting painful experiences, experiential cognitive methods to promote awareness, exercises similar to mindfulness, methods to increase one's the role of goals and values in patient choice, and to help people flexibly stick to commitments (McCracken, 2005).

The process will involve, two brief direct one-to-one contact sessions, one at the beginning and one at the end of the intervention, with convenient means according to each participant, as for example Skype, phone or face to face. Following the first one-to-one session there will be 8 short online sessions, with a duration of 20-30 minutes each. In accordance with ACT principles, participants will be encouraged to complete tasks between the online sessions. Particularly, they will be asked to

write on a diary weekly, which will include ratings for openness, awareness and engagement. Within the diary we will also ask participants to note changes, in medication, if any, and if the data is sufficient and relevant, we will include them in the final analysis. The completion of these tasks has been found to be predictive of CBT outcomes (Kazantzis, Whittington, & Dattilio, 2010; Mausbach, Moore, Roesch, Cardenas, & Patterson, 2010).

Post Intervention Evaluation

At the end, we will also have evaluation forms for treatment completers. They will be asked to answer a questionnaire on the acceptability of format, focus, and content of treatment; whether they found it helpful; any barriers to participation or barriers to benefits they could identify; acceptability of the assessment methods; and any views they might provide on maximizing access, participation, and effectiveness of the treatment in the future.

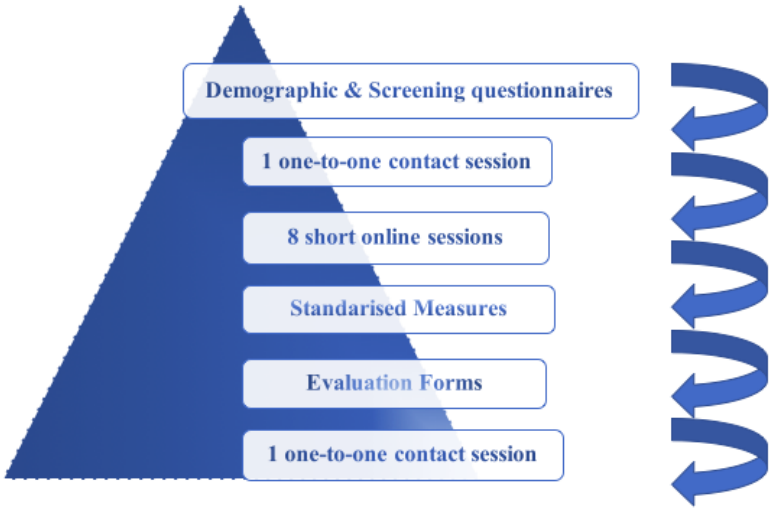

Figure 19: Outline of the intervention

Statistical Analysis

The distribution tool for the dissemination of the questionnaires and for raw data collection will be the BOS platform, and statistical data analysis will be performed using the SPSS software tool, particularly for the numerical rating data and standardized measures. Descriptive statistics will be used to display demographic data of the participants and standardised measures will be scored according to their standard instructions.

The final phase of the project will include calculating recruitment and retention rates and examining the data from the feasibility study to consider the appropriateness of measures chosen for examining effects of treatment. Descriptive statistics, such as frequencies and percentages of patients approached, screened, eligible, consented, and allocated to treatment will be computed. Reasons for non-consent, exclusion, and drop-out, at each stage of the study, will be recorded and reported. Adherence to the intervention will be reported using descriptive statistics. Acceptability and credibility ratings will also be examined to assure that at least 75% provide ratings above the midpoint on each of the relevant ratings, to indicate feasibility on this basis.

Dissemination

We will endeavour to publish this research in a peer-reviewed journal, present the findings at relevant conferences and the findings will also contribute to the doctoral thesis of the PhD student (Miss Aikaterini-Pinelopi Kioskli).

Withdrawal Criteria

Patients who consent and begin treatment but discontinue will be contacted to explore their reasons for discontinuing treatment or any barriers they encountered to participating. Participants have the right to withdraw from the research at any time without having to give a reason for doing so. Their right and access to their usual NHS treatment will not be compromised in any way if they

decide to withdraw. All study participants will notify the research team of their wish to withdraw, using the contact details provided in the Participant Information Sheet for this study. As indicated on the Informed Consent Form, all data collected before the point of withdrawal will be retained and analysed unless the participant requests otherwise. It will not be possible to withdraw a patient's data after data analysis.

Ethical Considerations

Patients may find completing questionnaires and treatment delivery burdensome or mildly stressful. However, we hope that this burden will be offset by having access to the treatment which will likely benefit their psychological wellbeing and increase their psychological flexibility. Participants will be reminded that they are free to withdraw from the study at any time. Participants will be fully informed about the intervention using the participant information sheet and a researcher will be on hand to answer any specific questions.

If participants require additional emotional support, they will be referred to their GP to consider possibly a psychologist or counsellor at the earliest possible time point. If there is an urgent risk to participant's mental or physical health, then they will be referred to their clinical care team, their General Practitioner or the emergency services immediately. If the members of the research team, involved in the treatment delivery, feel concerned about the level of distress of a participant; with the participant's permission, this will be disclosed to the clinical care team. Participants will also receive information on the support services of the Diabetes UK.

Fortnightly supervision meetings will occur with the researchers involved in the delivery of the intervention, this will include ensuring fidelity to the treatment and to assess and discuss patient progress. An appropriate treatment plan will be initiated.

Adverse Effects

Risk to participants are expected to be small based on extensive experiences of the methods used here with other populations. Participants may find the questionnaires or treatment mildly distressing. However, these effects are anticipated to be short lived, as participants will learn psychological techniques during the intervention that can help them manage negative emotions and diabetes better.

Potential Risks for Researchers

There are no identifiable risks for the researchers.

Regulatory Issues

Ethic Favourable Opinion and NHS R&D Permission

All Investigators will obtain HRA Approval, which combines the REC opinion and R&D permissions. The Chief Investigator will require a copy of the research team's current CV and GCP certificates, and letter of NHS permission before accepting participants into the study. On obtaining a favourable ethical opinion, any subsequent changes to the conduct, design or management of the study will be notified to the original approving REC and any other relevant regulatory authority via a substantial amendment. Changes to the study will not be implemented until REC approval has been obtained. NHS R&D Amendment permission from the participating sites will be required before any changes can be implemented at the applicable site. The CI will submit a final report to the sponsor and the approving REC. The research team, which have taken part in the development of the treatment and protocol, includes researchers with expertise in quantitative methods, developing and delivering psychological treatments to patients with chronic pain and diabetes.

Confidentiality and Data Management

The Chief Investigator (CI) and all members of the research team will preserve the confidentiality of participants taking part in the study and will work in accordance with the Caldicott Principles, Data Protection Act 1998, NHS Code of Confidentiality and any relevant NHS Trust organisational policies. The participating NHS sites will be bound to act in accordance with these applicable regulations. Research team members who are not part of the direct care team will not have access to patients' identifiable records without consent at any stage of research, including identification of eligible participants. All participants will be assigned an identification number (ID) and all collected data will be identified by the ID number. The consent form will contain patient identifiable information, including the name, contact details, and GP information. This information will be necessary to maintain contact with the participants throughout the feasibility study, in particular to arrange treatment delivery, and also to notify the GP of their participation in the study. A secure database of participants' Study ID, names and contact details will be maintained by the research team, accessed by a password and stored in a secure, restricted access folder at King's College London. The demographic, clinical, and psychological data will be stored in a separate database from the identifiable data.

All electronic data will be anonymised and stored in a restricted access folder on a password-protected computer at King's College London. Secure password-controlled access is restricted to the research team only. All identifiable data stored in paper files (signed consent forms) will be managed securely in restricted access, lockable cabinets at King's College London. Consent forms, containing identifiable information, will be stored separately from non-identifiable data. When the study is completed, all non-identifiable data will be archived at King's College London and held for seven years, in accordance with sponsor requirements.

Indemnity

The study is sponsored by King's College London, providing insurance for the study, through its own professional indemnity for research involving human participants and no-fault compensation and the Trust having a duty of care to patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient.

Sponsor

KCL will act as the main sponsor for this study and will adhere to the Research Governance Framework for Health and Social Care 2005 (2nd Edition), and any amendments or subsequent replacements. The study will be co-sponsored by GSTT.

Funding

This study is part of a PhD, funded by the Diabetes UK to Aikaterini-Pinelopi Kioskli. The views expressed are those of the authors and not necessarily those of the NHS or Diabetes UK. Participants will not receive any financial incentive.

Audits and Inspections

The study may be subject to inspection and audit by King's College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition). The participating NHS sites are required to comply with any requests for audit by the sponsor or applicable site R&I Office and ensure that the study documentation and information is available in the relevant site file. Copies of audit / monitoring reports will be sent to the sponsor R&I offices.

Amendments

There are no anticipated amendments to the study conduct, management and activities at this stage (pre-study preparation and planning June-September 2017). Authorisation will be sought from the study sponsor for any future substantial and non-substantial amendments arising during the course of the study, prior to submission to the HRA. Advice on amendments will be sought via: *http://www.nres.npsa.nhs.uk/applications/after-ethical-review/notification-of-amendments/*

Intellectual Property

Any intellectual property arising from the development, conduct and completion of this study will be owned by the study sponsor.

Study Management

The day-to-day management of the study will be co-ordinated by the CI and the trial management team. The team will also meet regularly, once a month, to discuss the overall running of the study including: rates of recruitment, adherence to the protocol, safety and confidentiality of patients. All serious adverse events related to the study will be reported to the study sponsor, ethics committee and relevant NHS R&I departments. The monitoring and auditing of the conduct of the research within the Trust lies with the R&I Office. The R&I Office, on behalf of the Sponsor, may monitor and conduct random audits on a selection of studies in its clinical research portfolio, or may conduct for-cause monitoring visits following an incident or a breach or GCP or protocol.

Deviations and Breaches

In the case of study deviations or serious breaches of protocol, study deviation forms will be completed and forwarded to the study sponsor.

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Appendix G: Participants' Information Sheet for Survey

Guy's and St Thomas' NHS
NHS Foundation Trust

Guy's and St Thomas' contact details:

Telephone: 020 7188 7188

E-mail: pals@gstt.nhs.uk

Information Sheet for Participants

Title of Project: The Development of Contextual Cognitive Behavioural Approach to painful diabetic neuropathy; revealing patients' perceptions and beliefs

We would like to invite you to participate in a study. This study seeks a more in-depth understanding of the patients' experiences and perspectives related to **painful diabetic neuropathy (PDN)**, to further develop an acceptable and effective psychological treatment for this condition. Before you decide whether to take part in this study, it is important that you understand why the research is being conducted and what is involved. Please take time to read the following information and feel free to ask if there is anything that is not clear or if you would like more information.

What is the purpose of this project?

This is part of a PhD project at King's College London. It is hoped that this study will improve our understanding of PDN. PDN is usually managed with medication. There has been little development or research into psychological treatments for neuropathic pain, in general, including PDN. However, existing evidence demonstrates that psychological treatments applied to chronic pain are beneficial, in terms of improving functioning in daily activities for people who participate. In the current study,

we assess the experience of pain from the perspective of people with PDN and examine their treatment needs and preferences.

Who is eligible to take part?

Participants will have to fulfil the following criteria to take part in the study:

- Confirmed diagnosis of diabetes.
- Presence of painful diabetic neuropathy.
- Aged at least 18 years.
- Willingness and ability to take part.

Why have I been invited?

You have been identified as a potential participant by your doctor because you have a confirmed diagnosis of diabetes and you suffer from neuropathic pain due to diabetes.

What will I have to do if I agree to take part?

Participants will have to answer ten short questionnaires, which overall will help the research team to collect demographic data, and assess pain intensity, certain attitudes toward pain, mood, and the impact of pain on participants' daily physical, social and work activities.

How much of my time will participation involve?

Participation should take no more than 45 minutes.

Will my participation in the project remain confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. You will be given this information sheet and a signed consent form to keep, if you wish. The information you provide is completely confidential and anonymous. Your responses to the

questionnaires will be used for the purpose of this project only. The results from the analyses of the combined data will be summarized and submitted for publication in an academic journal and also be presented in scientific conferences. No participants' identity will be included in these reports. The research team will only have access to patients' identifiable records after the participants have provided informed consent. KCL and GSTT, acting as sponsor and co-sponsor to this study, may also have access to the collected data for monitoring purposes. If data is transferred through optical media, it will be encrypted through password protection during transfer. When data will be stored on University computers, password-controlled access to the secure network will be restricted to the research team members only. The collected data will be kept for a maximum of 5 years. Any identifiable information from questionnaires will be removed. An ID number will be assigned to each completed questionnaire to ensure that data cannot be traced back to an individual. Participant data in paper (without identifying information) and consent forms in paper (with identifying information and contact details) will be stored separately and securely in restricted access, lockable cabinets at KCL. Your anonymised data will be shared with other researchers and may be used for other research purposes. At the end of the present survey you will be kindly asked if you like to take part to further research, if yes you will be asked to provide your contact details which will be stored from 6-12 months. Your contact details will only be used to help the research team get in touch with you for a future study. Nobody else will have access to your contact details.

What are the advantages of taking part?

You will have opportunity to share your thoughts of diabetes and neuropathy. The results from this survey will provide valuable input and will help in the development of an acceptable and potentially effective psychological treatment for people who suffer from painful diabetic neuropathy.

Are there any disadvantages of taking part?

We do not foresee any disadvantages of participating in this study, except that it does require some time. You do not have to answer any questions if you do not wish to.

Do I have to take part in the study?

No. It is entirely your decision as to whether you take part in this study. If you decide to take part, you will be asked to complete a consent form. Please note the deadline to request withdrawal of your data from the study will be four weeks after the end of data collection. It will not be possible to withdraw your data after analysis. If you wish you are free to withdraw at any time during the study period without giving a reason, even if you initially decided to take part without affecting your quality of treatment or medical care.

Will my GP and clinical care team be involved?

The research team is in no way connected with the team involved in your treatment and your decision to participate or not will in no way affect the standard of care you receive. Your personal GP will not be involved in the study, but they will be informed of your participation with your permission. Any contact with the research team will be logged in your medical history file, for example, on the day a member of the research team approaches you about the study, it will be recorded as *'approached for participation and given participant information sheet'*. Additionally, you will receive a copy of the signed consent form and another copy will be added to your medical file, if you decide to take part in the study.

What will happen to the results of the research study?

The study will be presented at scientific conferences and be written up for publication in scientific journals. We will provide you with a summary sheet of the results, if you wish.

Who should I contact for further information?

If you have any questions or require more information about this study, please contact me using the following contact details: Name: Miss Aikaterini-Pinelopi Kioskli (PhD candidate), Email: aikaterini.kioskli@kcl.ac.uk, Telephone: +44 (0) 2071880188

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [Professor Lance M. McCracken, Email: lance.mccracken@kcl.ac.uk, Telephone: +44 (0) 207 188 5410, Health Psychology Section, Psychology Department, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), Guy's Campus, London, SE1 9RT]. If you remain unhappy and wish to complain formally, you can do this through the Guy's and St Thomas' Patients Advice and Liaison Service (PALS) on 020 7188 8801, pals@gstt.nhs.uk. The PALS team are based in the main entrance on the ground floor at St Thomas' Hospital and on the ground floor at Guy's Hospital in the Tower Wing. In the event that something does go wrong and you are harmed during the research you may have grounds for legal action for compensation against Guy's and St Thomas' NHS Foundation Trust and/or King's College London but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Thank you for reading this information sheet and for considering taking part in this study!

Appendix H: Participants' Consent Form for Survey

Guy's and St Thomas' contact details:

Telephone: 020 7188 7188

E-mail: pals@gstt.nhs.uk

CONSENT FORM

Title of Project: The Development of Contextual Cognitive Behavioural Approach to painful diabetic neuropathy; revealing patients' perceptions and beliefs

Please initial box

1. I confirm that I have read the information sheet **dated 8.1.2018 version 2** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers. ☐
4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from King's College London, regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I agree to my General Practitioner being informed of my participation in the study. ☐
6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person Taking consent	Date	Signature

Appendix I: Questionnaire Pack for Survey and Feasibility Study

Please read each question carefully. We kindly ask you to answer the questions as honestly and as quickly as possible. There are no right or wrong answers to these questions. We are mostly interested in your own experiences and circumstances. The information that you provide in this form is **completely confidential** and **anonymous** and will not be shared with anyone outside the clinical or research team without your expressed consent. Your participation is voluntary, and you are free to withdraw at any time without giving any reason. If you have any difficulty completing these questionnaires or any further questions, please contact a member of the research team.

Screening Questions

Do you have a confirmed diagnosis of diabetes from your physician? **Yes/No**

Do you have a confirmed diagnosis of neuropathy (or nerve pain or painful diabetic neuropathy or neuropathic pain or polyneuropathy) from your physician? **Yes/No**

Pain History

Duration of pain (please state): _____Years _____ Months

Pain location

Where is the main or worst pain (i.e. legs, hand)? _____

Demographic Questionnaire

(Please tick/circle the answer of your choice or provide information required)

What is your sex? Female/Male/Other

How old are you? ___ years' old

How many years of education have you completed?

(Please provide total years completed counting from primary school-not school "leaving age")

_____years

What is your ethnic group? *Please tick the appropriate box*

White	British		**Black or British Black**	Caribbean		**Chinese or other ethnic group**	Chinese	
	Irish			African			Other	
	Other			Other				
Mixed	White and Black Caribbean		**Asian or Asian British**	Indian				
	White and Black African			Pakistani				
	White and Asian			Bangladeshi				
	Other			Other				

Do you live:

alone	
with partner	
with child/children	
with partner and child/children	
with other relatives	
with friends/flatmates	

What is your <u>present</u> work status? *Please tick ONE box:*

Employed	Full time	
	Part time due to pain	
	Part time by choice/other reasons	
	Volunteer/unpaid	
	Carer	
	Homemaker	
Unemployed	Because of pain	
	Unrelated to pain problems/other	
Student/Training	Full time	
	Part time due to pain	
	Part time by choice/other reasons	
Retired		
Other (please		

Douleur Neuropathique 4 (DN4) – Questionnaire

To estimate the probability of neuropathic pain, please answer yes or no for each item of the following four questions.

Does the pain have one or more of the following characteristics?

Burning ..... ❑

Painful cold ..... ❑

Electric shocks ..... ❑

Is the pain associated with one or more of the following symptoms in the same area?

Tingling ..... ❑

Pins and needles ..... ❑

Numbness ..... ❑

Itching .....❑

Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?

Hypoesthesia to touch .....❑

Hypoesthesia to pinprick .....❑

In the painful area, can the pain be caused or increased by:

Brushing? .....❑

Pain Scale

Please indicate on the scale below the number between **0 and 10** that best describes your pain. 0 indicates no pain at all and 10 indicates the worst possible pain.

How intense is your pain right now?

0	1	2	3	4	5	6	7	8	9	10
□	□	□	□	□	□	□	□	□	□	□

none as bad as you can imagine

How intense was your pain on average last week?

0	1	2	3	4	5	6	7	8	9	10
□	□	□	□	□	□	□	□	□	□	□

none as bad as you can imagine

How distressing is your pain right now?

0	1	2	3	4	5	6	7	8	9	10
□	□	□	□	□	□	□	□	□	□	□

none as bad as you can imagine

How distressing was your pain on average last week?

0	1	2	3	4	5	6	7	8	9	10
□	□	□	□	□	□	□	□	□	□	□

none as bad as you can imagine

Work and Social Adjustment Scale (WSAS)

Rate each of the following questions on a 0 to 8 scale: 0 indicates no impairment at all and 8 indicates very severe impairment.

1. **Because of my condition, my ability to work is impaired.**

   0 1 2 3 4 5 6 7 8

   No Impairment Very Severe Impairment

2. **Because of my condition, my home management (cleaning, tidying, shopping, cooking, looking after home or children, paying bills) is impaired.**

   0 1 2 3 4 5 6 7 8

   No Impairment Very Severe Impairment

3. **Because of my condition, my social leisure activities (with other people, such as parties, bars, clubs, outings, visits, dating, home entertainment) are impaired.**

   0 1 2 3 4 5 6 7 8

   No Impairment Very Severe Impairment

4. **Because of my condition, my private leisure activities (done alone, such as reading, gardening, collecting, sewing, walking alone) are impaired.**

   0 1 2 3 4 5 6 7 8

   No Impairment Very Severe Impairment

5. **Because of my condition, my ability to form and maintain close relationships with others, including those I live with, is impaired.**

   0 1 2 3 4 5 6 7 8

   No Impairment Very Severe Impairment

Patient Health Questionnaire (PHQ-9)

Over the **last 2 weeks**, how often have you been bothered by any of the following problems (please circle your answer)?

		Not at all	Several days	More than half the days	Nearly every day
1	**Little interest or pleasure in doing things.**	0	1	2	3
2	**Feeling down, depressed, or hopeless.**	0	1	2	3
3	**Trouble falling or staying asleep, or sleeping too much.**	0	1	2	3
4	**Feeling tired or having little energy.**	0	1	2	3
5	**Poor appetite or overeating.**	0	1	2	3
6	**Feeling bad about yourself—or that you are a failure or have let yourself or your family down.**	0	1	2	3
7	**Trouble concentrating on things, such as reading the newspaper or watching television.**	0	1	2	3
8	**Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual.**	0	1	2	3
9	**Thoughts that you would be better off dead, or of hurting yourself in some way.**	0	1	2	3

10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people (please circle your answer)**?**

Not difficult at all

Somewhat difficult

Very difficult

Extremely difficult

Committed Action Questionnaire

Below you will find a list of statements. Please rate the truth of each statement as it applies to you by selecting a number. Use the following rating scale to make your choices. For instance, if you believe a statement is "Always True", you would select number 6.

0	1	2	3	4	5	6
Never true	**Very rarely true**	**Seldom true**	**Sometimes true**	**Often true**	**Almost always true**	**Always true**

1	**I can remain committed to my goals even when there are times that I fail to reach them.**	0	1	2	3	4	5	6
2	**When a goal is difficult to reach, I am able to take small steps to reach it.**	0	1	2	3	4	5	6
3	**I prefer to change how I approach a goal rather than quit.**	0	1	2	3	4	5	6
4	**I am able to follow my long terms plans including times when progress is slow.**	0	1	2	3	4	5	6
5	**I find it difficult to carry on with an activity unless I experience that it is successful.**	0	1	2	3	4	5	6
6	**If I feel distressed or discouraged, I let my commitments slide.**	0	1	2	3	4	5	6
7	**I get so wrapped up in what I am thinking or feeling that I cannot do the things that matter to me.**	0	1	2	3	4	5	6
8	**If I cannot do something my way, I will not do it at all.**	0	1	2	3	4	5	6

Chronic Pain Acceptance Questionnaire (CPAQ)

Below you will find a list of statements. Please rate the truth of each statement as it applies to you by selecting a number. Use the following rating scale to make your choices. For instance, if you believe a statement is "Always True", you would select number 6 next to that statement.

0	1	2	3	4	5	6
Never true	Very rarely true	Seldom true	Sometimes true	Often true	Almost always true	Always true

1.I am getting on with the business of living no matter what my level of pain is.	0	1	2	3	4	5	6
2. Although things have changed, I am living a normal life despite my chronic pain.	0	1	2	3	4	5	6
3. I lead a full life even though I have chronic pain.	0	1	2	3	4	5	6
4. Keeping my pain level under control takes first priority whenever I am doing something.	0	1	2	3	4	5	6
5. Before I can make any serious plans, I have to get some control over my pain.	0	1	2	3	4	5	6
6. When my pain increases, I can still take care of my responsibilities.	0	1	2	3	4	5	6
7. I avoid putting myself in situations where pain might increase.	0	1	2	3	4	5	6
8. My worries and fears about what pain will do to me are true.	0	1	2	3	4	5	6

Self-Experiences Questionnaire (SEQ)

Below you will find a list of statements. Please rate the truth of each statement as it applies to you. Use the following rating scale to make your choices. For instance, if you believe a statement is 'Always True,' you would select number 6 next to that statement.

0 Never true	1 Very rarely true	2 Seldom true	3 Sometimes true	4 Often true	5 Almost always true	6 Always true

1. Although I can get caught up with my own thoughts, emotions and sensations, I can also separate myself from them.	0	1	2	3	4	5	6
2. I am able to step back from my emotions and observe them from a separate point of view.	0	1	2	3	4	5	6
3. I am able to separate myself from my thoughts and feelings.	0	1	2	3	4	5	6
4. I have thoughts and feelings but am not defined as just my thoughts and feelings.	0	1	2	3	4	5	6
5. I can experience a distinction between my experiences and the "I" who notices these experiences.	0	1	2	3	4	5	6
6. I can actually see that I am not my thoughts.	0	1	2	3	4	5	6
7. I experience myself as more than my thoughts and feelings.	0	1	2	3	4	5	6
8. The health, appearance, and feelings of my body change, but the sense of myself who is aware of these changes is the same.	0	1	2	3	4	5	6
9. When I feel distressed, I can notice what is happening without being overwhelmed.	0	1	2	3	4	5	6
10. I can notice what I am thinking and feeling without getting too caught up in these experiences.	0	1	2	3	4	5	6

11.Above all my experiences, there is a sense of myself who is noticing them.	0	1	2	3	4	5	6
12.I can notice that my mind is thinking from moment to moment.	0	1	2	3	4	5	6
13.I can observe experiences in my body and mind as events that come and go.	0	1	2	3	4	5	6
14.I am able to remain aware of my experiences from moment to moment.	0	1	2	3	4	5	6
15.My roles change depending on time, place and setting, but the sense of myself who has the roles stays the same.	0	1	2	3	4	5	6

Cognitive Fusion Questionnaire (CFQ7)

Below you will find a list of statements. Please rate how true each statement is for you by circling a number next to it. Use the scale below to make your choice.

1	2	3	4	5	6	7
Never true	Very seldom true	Seldom true	Sometimes true	Frequently true	Almost always true	Always true

1. My thoughts cause me distress or emotional pain.	1	2	3	4	5	6	7
2. I get so caught up in my thoughts that I am unable to do the things that I most want to do.	1	2	3	4	5	6	7
3. I over-analyse situations to the point where it's unhelpful to me.	1	2	3	4	5	6	7
4. I struggle with my thoughts.	1	2	3	4	5	6	7
5. I get upset with myself for having certain thoughts.	1	2	3	4	5	6	7
6. I tend to get very entangled in thoughts.	1	2	3	4	5	6	7
7. It's such a struggle to let go of upsetting thoughts even when I know that letting go would be helpful.	1	2	3	4	5	6	7

If you would also like to take part in further research, please provide your contact details below:

Thank you for taking part in this survey! Your input is very much valuable to us.

Guy's and St Thomas' NHS
NHS Foundation Trust

Guy's and St Thomas' contact details:

Telephone: 020 7188 7188

E-mail: pals@gstt.nhs.uk

Appendix J: Participants' Information Sheet for Feasibility Study

Guy's and St Thomas' NHS
NHS Foundation Trust

Guy's and St Thomas' contact details:

Telephone: 020 7188 7188

E-mail: pals@gstt.nhs.uk

KING'S College LONDON
University of London

IRAS No 243486; REC Reference Number: 17/LO/2047

INFORMATION SHEET FOR PARTICIPANTS

The Development of Contextual Cognitive Behavioural Approach to painful diabetic neuropathy: A feasibility study

You are being invited to take part in a research study. **Please read this information carefully to understand why this research is being done and what your participation will involve.** Discuss this information with family members or friends or your doctor if you wish. Do not hesitate to contact the research team if anything is unclear or if you would like more information. **If you are happy to participate please complete the consent form and screening questionnaire and return them to the researcher via the freepost envelope or Skype or in-person.**

Who is conducting the study?

This study is being conducted as part of the main researcher's (Miss Aikaterini-Pinelopi Kioskli) doctoral studies and supervised by Professor Lance M. McCracken and Dr. Kirsty Winkley at King's College London, the Institute of Psychiatry, Psychology and Neuroscience (IoPPN).

What is the purpose of the study?

People with diabetes often experience a type of pain called Painful Diabetic Neuropathy (PDN). PDN is described as a stabbing, burning, pricking, or aching sensation affecting the toes, feet, and legs.

This type of pain can interfere with walking, sleep, mood and overall quality of life. Although medication may offer some short-term improvement in this pain, this is a chronic condition for the majority of the patients and the pain typically remains a problem. Our research team aims to assess the acceptability and potential benefits of a psychological treatment for people with PDN.

Who is eligible to take part?

Participants will have to fulfil the following criteria in order to take part in the study:

- Confirmed diagnosis of diabetes.
- Presence of painful diabetic neuropathy, for the last three months or more (a screening questionnaire has been added to verify that you suffer from neuropathy).
- Aged at least 18 years.
- Willingness and ability to take part.
- Have computer literacy.

Why have I been invited?

You have been identified as a potential participant by your doctor because you have a confirmed diagnosis of diabetes and you suffer from neuropathic pain due to diabetes. In order to ensure that you are eligible to take part in the study, you will need to complete a screening questionnaire to check that you meet the study requirements. Once you return the completed screening questionnaire and consent form, a member of the research team will notify you of your eligibility.

Do I have to take part?

No. It is entirely your decision as to whether you take part in this study. If you decide to take part, you will be asked to complete a consent form either face to face or through Skype chat. Please note

the deadline to request withdrawal of your data from the study will be four weeks after the end of data collection. It will not be possible to withdraw your data after analysis. If you wish you are free to withdraw at any time during the study period without giving a reason, even if you initially decided to take part without affecting your quality of treatment or medical care.

What will happen to me if I take part?

As part of this study, you will continue to receive treatment as usual from your doctor as you normally do. However, you will also have the opportunity for an additional psychological treatment called Acceptance and Commitment Therapy (ACT). The ACT treatment includes treatment processes of acceptance, cognitive defusion, mindfulness, and values-based action. Methods will include practice to deal with painful experiences, to improve awareness, to identify and work on goals, and to better stick to commitments. The process will involve, two, brief, one-to-one contact sessions, one at the beginning and one at the end of the intervention, in a way that is convenient for you, including Skype, phone, or face to face in person. Following the first one-to-one session there will be eight short online sessions, about 20-30 minutes each. You will also be asked to complete some tasks between the sessions, in particular to record your progress briefly and any changes at your medication (i.e. type of drug, dose) in a diary weekly so that you can keep track of your developing skills.

Will my GP and clinical care team be involved?

The research team is not directly connected with the team involved in your treatment and your decision to participate or not will in no way affect your medical care and treatment that you receive. Your personal GP will not be involved in the study, but they will be informed of your participation with your permission. Any contact with the research team will be logged in your medical history file, for example, on the day a member of the research team approaches you about the study, it will be recorded as *'approached for participation and given participant information sheet'*.

Will you compensate me for my time?

Unfortunately, due to limited funding, we are unable to compensate you for your time. However, we greatly appreciate your help and involvement and would like to thank you in advance for your time. At the conclusion of the study, if you are interested, we will also provide you with a summary the main findings when they are available.

Are there any costs?

There are no costs to participants associated with the project.

What are the possible disadvantages and risks of taking part?

We believe that the risks involved in participating are minimal. It is possible that you might find it mildly distressing during the study. However, this effect is anticipated to be short lived, as you will learn psychological techniques during the intervention that can help you manage uncomfortable emotions, enhance your "psychological flexibility," and to be mindful of your thoughts and accept your feelings. Should you become distressed during or after the intervention, you will have the opportunity to notify the member of the research team (please find contact details below). At this time, you can be helped to contact a suitable source of support or you may be encouraged to talk with your clinical care team for more information in this regard. If you require additional emotional support, again an appropriate referral can be made. If there is an urgent risk to your mental or physical health, you will be referred to the clinical care team, your General Practitioner or the emergency services right away.

What are the possible benefits of taking part?

Previous studies suggest that your painful symptoms will be helped by the ACT treatment, however we cannot guarantee improvements. Your information will help us gain more knowledge regarding the treatment used in the study, particularly whether it is acceptable, feasible, and helpful. At the

end of the intervention we have added a questionnaire which will reflect the potential changes on your quality of life after treatment. At the conclusion of the project, we will send you a summary describing the major findings and alerting you to any research publications we have generated from the project.

Will my taking part in the study be kept confidential?

Yes. All information about your participation in this study will be kept confidential in accordance with the Data Protection Act 1998. All participants will be assigned an identification number (ID) and all collected data will be identified by the ID number, making it anonymous. Your personal information, such your name and contact details will be stored separately from all the collected data. Your information will be stored on secure computers, locked within offices and in locked file cabinets, and will only be available to members of the research team. This information will only be used for the purposes of the current study. The information you provide on the consent form (your name, contact details, and GP registration) will be destroyed at the end of the study. Your study data will be retained for a maximum of seven years and subsequently disposed of securely. Your anonymised data will be shared with other researchers and may be used for other research purposes.

What will happen if I don't want to carry on with the study?

You are free to withdraw from the study at any time without having to give a reason even if you initially decided to take part.

What will happen to the results of the research study?

The research data will be kept for a maximum of 7 years. KCL and GSTT, acting as sponsor and co-sponsor in this study, will also have access to the collected data for monitoring purposes. The results will be used to help researchers understand whether an ACT programme for PDN is acceptable,

feasible, and beneficial for patients. The study will be presented at scientific conferences and be written up for publication in scientific journals. We will provide you with a summary sheet of the results, if you wish.

Who is organising and funding the research?

The study is funded by Diabetes UK. It is being organized and conducted by researchers from the Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology, and Neuroscience, at King's College London.

Has this study obtained ethical approval?

Yes, this study has been reviewed by the London Surrey Rec.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [Professor Lance M. McCracken, Email: lance.mccracken@kcl.ac.uk, Telephone: +44 (0) 207 188 5410, Health Psychology Section, Psychology Department, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), Guy's Campus, London, SE1 9RT]. If you remain unhappy and wish to complain formally, you can do this through the Guy's and St Thomas' Patients Advice and Liaison Service (PALS) on 020 7188 8801, pals@gstt.nhs.uk. The PALS team are based in the main entrance on the ground floor at St Thomas' Hospital and on the ground floor at Guy's Hospital in the Tower Wing. In the event that something does go wrong and you are harmed during the research you may have grounds for legal action for compensation against Guy's and St Thomas' NHS Foundation Trust and/or King's College London but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

What if I have questions about the project? Contact details for further information

If you have any questions or would like to discuss further your potential involvement in this study, please use the contact details below to get in touch with the research team.

Name: Miss Aikaterini-Pinelopi Kioskli

Job title: Doctoral Student

Email address: aikaterini.kioskli@kcl.ac.uk

Address: Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology, and Neuroscience, Kings College London, 5th Floor Bermondsey Wing, Guys Campus, London SE1 9RT

OR

Name: Professor Lance M. McCracken

Job title: Chief Investigator (PhD Supervisor)

Email address: lance.mccracken@kcl.ac.uk

Address: Health Psychology Section, Department of Psychology, Institute of Psychiatry, Psychology, and Neuroscience, Kings College London, 5th Floor Bermondsey Wing, Guys Campus, London SE1 9RT

OR

Name: Dr. Kirsty Winkley

Job Title: Co-Investigator (PhD Supervisor)

Email Address: kirsty.winkley@kcl.ac.uk

Address: King's College London & Institute of Psychiatry, Psychology & Neuroscience, Department of Psychological Medicine, Weston Education Centre, Cutcombe Road, London, SE5 9RJ

Study Title: The Development of Contextual Cognitive Behavioural Approach to painful diabetic neuropathy: A feasibility study

IRAS Number: 224386

Supplementary Patient Information Sheet on the Use of Data

King's College London and Guy's and St Thomas' NHS Foundation trust are the co-sponsors for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. King's College London and Guy's and St Thomas' NHS Foundation trust will keep identifiable information about you for 7 years after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information

https://www.guysandstthomas.nhs.uk/research/patients/about.aspx

www.kcl.ac.uk/innovation/research/support/ethics/how-does-gdpr-affect-ethics/king's-college-london-statement-on-use-of-personal-data-in-research.aspx

Guy's and St Thomas' Hospital will collect information from you for this research study in accordance with our instructions. Guy's and St Thomas' NHS Foundation trust will use your name, and contact details to contact you about the research study, and make sure that relevant information about the

study is recorded for your care, and to oversee the quality of the study. Individuals from King's College London, Guy's and St Thomas' NHS Foundation trust and regulatory organisations may look at your research records to check the accuracy of the research study. The only people in King's College London who will have access to information that identifies you will be people who need to contact you to audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

Appendix K: Participants' Consent Form for Feasibility Study

KING'S College LONDON

Guy's and St Thomas' NHS
NHS Foundation Trust

Guy's and St Thomas' contact details:

Telephone: 020 7188 7188

E-mail: pals@gstt.nhs.uk

CONSENT FORM

Title of Project: The Development of Contextual Cognitive Behavioural Approach to painful diabetic neuropathy: A feasibility study

Name of Researcher: Aikaterini-Pinelopi Kioskli

Please initial box

1. I confirm that I have read the information sheet **dated 26.6.2018 version 3** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers. ☐
4. I agree to my General Practitioner being informed of my participation in the study. ☐
5. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from King's College London, regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records ☐
6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix L: Email to Participants

This was the first email I sent to participants after they made contact and expressed their interest. The rest of the communication was conducted through the online treatment platform called ACT4PAIN or via Skype.

Subject: Online psychological treatment for individuals with painful diabetic neuropathy

Dear <Name>,

Thank you for getting in touch and for your interest in our psychological treatment. My name is Kitty Kioskli and I am part of a research team in King's College London. My research team and I designed an online psychological treatment for individuals who suffer from painful diabetic neuropathy (neuropathy/nerve pain due to diabetes). This treatment will be completely free of charge since it is part of my PhD. This is a feasibility study which means that our main aims are to see investigate if this treatment would be acceptable and effective. If you are interest to take part the steps, you need to take are simple:

Step 1: The first session is meant to be by phone or any other means preferable to you (i.e. Skype). After you read the information sheet (which you may find attached) and information provided in this email, if you decide that you would be interested in taking part, please respond to this email to arrange our first session at your convenience.

Step 2: After completing our first session, I will kindly ask you to complete a baseline questionnaire through the following link: https://kings.onlinesurveys.ac.uk/baseline_questionnaire (it will ask you for a unique ID and yours is: **XXX**).

Step 3: As soon as you complete the baseline questionnaire, I will register you as a patient in our online platform (called ACT4PAIN).

This treatment program is a form of cognitive behavioral therapy (CBT), and is meant to be very practical. We know it takes skills, flexibility, persistence and focus to deal effectively with chronic pain, and this is what this treatment is meant to help with! My goals, as a therapist, are to help you reach your goals so that pain does not stop you in your everyday life. My other goal is to be there as a support behind the set of exercises we provide. In that sense my goal is to form a team with you and help you succeed!

There are just a couple of guidelines here: This treatment is meant to last **5 weeks**, you need to complete **8 online sessions** in total, each session lasts **30 minutes**. We have designed the treatment to be completed in this timeframe to help keep us focused and on track with your goals, so it is important to follow this schedule. You will be able to message me throughout the treatment via the online platform and I will also message you every time you complete a session!

Step 4: When you successfully complete your treatment, I will send you a final online questionnaire to answer. This will help us compare your answers from the baseline questionnaire and will reveal if there are any differences to your pain levels and everyday life.

Please find attached the Participant's Information Sheet for more details. I am on your disposal for any further queries.

Kind regards,

Kitty Kioskli, PhD Candidate
King's College London, Health Psychology Section
Psychology Department, Institute of Psychiatry, Psychology & Neuroscience (IoPPN)
5th Floor Bermondsey Wing
Guy's Hospital Campus
London, SE1 9RT

Appendix M: Surrey Research Ethics Committee (REC) Approval

NHS
Health Research Authority

London - Surrey Research Ethics Committee
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

29 January 2018

Professor Lance McCracken
Psychology Department Institute of Psychiatry, Psychology & Neuroscience King's College London
5th Floor Bermondsey Wing Guy's Campus
London, UK
SE1 9RT

Dear Professor McCracken

Study title:	**The Development of Contextual Cognitive Behavioural Approach to Painful Diabetic Neuropathy**
REC reference:	**17/LO/2047**
IRAS project ID:	**224386**

Thank you for your letter of 15 January 2018, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Draft of Advertisment]	Version 1	28 September 2017
Copies of advertisement materials for research participants [Emails for organisations]	Version 1	28 September 2017
Covering letter on headed paper		08 January 2018
GP/consultant information sheets or letters [GP Letter-Survey]	Version 1	28 September 2017
GP/consultant information sheets or letters [GP Letter-Trial]	Version 1	28 September 2017
IRAS Application Form [IRAS_Form_08112017]		08 November 2017
IRAS Application Form XML file [IRAS_Form_08112017]		08 November 2017
IRAS Checklist XML [Checklist_20112017]		20 November 2017
IRAS Checklist XML [Checklist_09012018]		09 January 2018
Letter from funder [Letter from funder]		11 January 2017
Other [KCL indemnity policy 2017-2018]	Version 1	24 July 2017
Other [Certificate of Employer's Insurance]	Version 1	08 January 2018
Other [Insurance certificate]	Version 1	18 July 2017
Participant consent form [Consent Form-Survey]	Version 1	28 September 2017

Participant consent form [Consent Form-Trial]	Version 1	28 September 2017
Participant information sheet (PIS) [Participants Information Sheet-Survey]	Version 1	28 September 2017
Participant information sheet (PIS) [Participants Information sheet-Trial]	Version 1	28 September 2017
Participant information sheet (PIS) [Participants Information Sheet-Survey]	Version 2	08 January 2018
Participant information sheet (PIS) [Participants Information sheet-Trial]	Version 2	08 January 2018
Research protocol or project proposal [Protocol]	Version 1	28 September 2017
Research protocol or project proposal [Protocol]	Version 2	08 January 2018
Summary CV for Chief Investigator (CI) [CI CV]		28 September 2017
Summary CV for student [Student's CV]		18 November 2017
Summary CV for supervisor (student research) [Second's Supervisor CV]		18 November 2017
Validated questionnaire [Validated Questionnaires]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
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HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/LO/2047	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

PP
Mrs Chrissie Lawson
Chair

Copy to: *Mr. Keith Brennan*
Miss Jennifer Boston, Guy's and St Thomas NHS Foundation Trust

Appendix N: Letter of Access

Guy's and St Thomas' NHS
NHS Foundation Trust

Aikaterini-Pinelopi Kioskli
53 Henley Drive
London
SE1 3AR

Our ref: LOA 826

Date: 16/02/2018

Dear Kitty,

Letter of access for: The Development of Contextual Cognitive Behavioural Approach to Painful Diabetic Neuropathy
R&D Reference: 224386
REC Reference: 17/LO/2047

This letter confirms your right of access to conduct research through Guy's and St Thomas's NHS Foundation Trust for the purpose and on the terms and conditions set out below. This right of access commences on the **16/02/2018** and ends on the **01/02/2020** unless terminated earlier in accordance with the clauses below.

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Principal Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at Guy's and St Thomas's NHS Foundation Trust has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out. The research has not been identified as being subject to Criminal Records Bureau Disclosure and therefore you should not undertake any work which involves unsupervised contact with children or vulnerable adults.

You are considered to be a legal visitor to Guy's and St Thomas's NHS Foundation Trust premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee.

While undertaking research through Guy's and St Thomas's NHS Foundation Trust you will remain accountable to King's Colle London. Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

You must act in accordance with Guy's and St Thomas's NHS Foundation Trust policies and procedures, which are available to you upon request, and the Research Governance Framework.

You are required to co-operate with Guy's and St Thomas's NHS Foundation Trust in discharging its duties under the Health and Safety at Work etc Act 1974 and other

health and safety legislation and to take reasonable care for the health and safety of yourself and others while on Guy's and St Thomas's NHS Foundation Trust premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and *strictly confidential* at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice (http://www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution. You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

Guy's and St Thomas's NHS Foundation Trust will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.

Yours sincerely,

LArnold

Lauren Arnold
R&D Facilitator (non-commercial team)

Cc: HR department of Substantive Employer

Appendix O: Other Publications and Accepted Abstracts

Peer-Reviewed Papers:

Scott, W., Arkuter, C., Kioskli, K., Kemp, H., McCracken, L. M., Rice, A. S., & de C Williams, A. C. (2018). Psychosocial Factors Associated with Persistent Pain in People with HIV: A Systematic Review with Meta-Analysis. Pain, 159(12), 2461-2476. https://doi.org/10.1097/j.pain.0000000000001369

Conference Presentations:

Date/Venue: 14-15 March 2018, London, UK

Conference: Diabetes UK Professional Conference

Type of presentation: Poster

Category: Psychological Care

Abstract

Psychosocial factors associated with painful diabetic neuropathy: a systematic review

A.P. Kioskli[1], W. Scott[1,3], S. Kylakos[4], K. Winkley[2], L. M. McCracken[1,3]

[1] King's College London, Health Psychology Section, Psychology Department, Institute of Psychiatry, London, UK

[2] King's College London, Department of Psychological Medicine, Institute of Psychiatry, London, UK

[3] Guy's and St Thomas' NHS Foundation Trust, London, UK, [4] City, University of London, London, UK

Aims: Despite the pressing need to investigate the role of psychological factors in the experience of chronic pain, less is known about the role of psychological factors in Painful Diabetic Neuropathy (PDN). We aimed to summarise all the psychological interventions, psychosocial factors and pain outcomes related to PDN, within the literature, and assess their methodological quality.

Methods: Eight electronic databases, thematically relevant reviews and associated reference lists were systematically searched to identify all studies examining a psychological intervention or psychosocial factors associated with PDN patients. The methodological quality of the eligible articles was assessed by the Downs and Black, (1998) quality assessment tool. Narrative synthesis was undertaken to summarise the data from the included studies.

Results: From 2,919 potentially relevant titles 22 studies were included in this systematic review. Associations between pain and psychosocial variables and treatment outcomes were examined. Three psychological interventions were identified and 19 survey studies. Different methods including questionnaires and self-reports were adopted to assess the effects of psychosocial variables in pain. Depression, anxiety and quality of life were the most commonly studied independent variables within this literature.

Conclusions: The current review suggests that depression, anxiety, impaired quality of life and disturbed sleep are consistently associated with pain. In light of the different psychological factors identified, it would be useful for future research to be undertaken in the context of a guiding theoretical model to understand how these psychological factors might work together and how these might be addressed within psychological treatments to improve outcomes for people with PDN.

Date/Venue: 15-18 May 2018, Malvern, UK

Conference: The 17th Malvern Diabetic Foot Conference

Type of presentation: Oral

Funding: This presentation was funded through a conference grant (£300) by the 'Doctoral Studies' at King's College London.

Abstract

A systematic review of psychological interventions and modifiable psychosocial factors associated with neuropathic pain due to diabetes

A.P. Kioskli[1], W. Scott[1, 3], K. Winkley[2], L. M. McCracken[1, 3]

[1] King's College London, Health Psychology Section, Psychology Department, Institute of Psychiatry, London, UK

[2] King's College London, Department of Psychological Medicine, Institute of Psychiatry, London, UK

[3] Guy's and St Thomas' NHS Foundation Trust, London, UK

Background and Aims: Painful Diabetic Neuropathy (PDN) is a multi-dimensional condition arising from diabetes and is considered very difficult to diagnose and treat. This systematic review aimed to identify the studies applying psychological interventions or investigating modifiable psychosocial factors related to pain outcomes, summarise the evidence and assess the methodological quality of these studies.

Methods: Eight electronic databases were searched: Medline, Embase, PsycInfo, Cinahl, Web of Science, ISRCTN registry, ClinicalTrials.gov registry, and EU Clinical Trials registry. Also, the reference lists of all included papers were investigated thoroughly to identify any additional eligible papers.

Results: Twenty-two studies (twenty-four papers) were included in this systematic review suggesting that depression and anxiety are the most studied independent variables, and quality of life the most studied dependent variable within the literature. Most studies had medium methodological quality.

Conclusions and Future Work: Few modifiable psychosocial factors have been studied within the literature and fewer psychological treatments have been developed for PDN. It would be useful for future research to consider the development of a theoretical framework which will encompass these modifiable psychosocial factors to develop acceptable and effective psychological interventions for the PDN population.

Date/Venue: 6-8 March 2019, Liverpool, UK

Conference: Diabetes UK Professional Conference

Type of presentation: Oral & Poster

Category: Psychological Care

Abstract

Psychological flexibility processes in adults with painful diabetic neuropathy and suitability of Acceptance and Commitment Therapy: A cross-sectional survey

K Kioskli[1], K Winkley[2], LM McCracken[1,3]

[1] King's College London, Health Psychology Section, Institute of Psychiatry Psychology and Neuroscience, London, United Kingdom

[2] King's College London, Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care, London, United Kingdom

[3] Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

Aims: Painful diabetic neuropathy (PDN) is a distressing and disabling condition. However, there is relatively little research into the role of psychological variables related to PDN. The aim of this study was to investigate the association between psychological flexibility (PF) and daily functioning and distress in people with painful diabetic neuropathy (PDN).

Methods: This cross-sectional study included 225 participants (mean age 52.05 $\pm$ 12.06) who were recruited from hospital services and online.

Results: In correlation analyses acceptance of pain negatively correlated to pain distress, $r=-0.22$, $p<0.01$, functional impairment, $r=-0.28$, $p<0.01$, depression severity, $r=-0.22$, $p<0.01$, and depression impact, $r=-0.22$, $p<0.01$. Cognitive fusion positively correlated with functional impairment, $r=0.24$, $p<0.01$, depression severity, $r=0.37$, $p<0.01$, and depression impact, $r=0.21$, $p<0.01$. Committed action also negatively correlated with functional impairment, $r=-0.21$, $p<0.01$, depression severity, $r=-0.37$, $p<0.01$ and depression impact, $r=-0.21$, $p<0.01$. In regression analyses, the combination of the four variables representing PF accounted for significant variance in all the equations except in pain distress. In the depression severity equation, cognitive fusion and committed action accounted for 13.3% of variance. In the depression impact equation, committed action and self-as-context accounted for 7.7% of variance.

Conclusions: PF processes seem to participate in processes of interaction between pain, emotional experiences, thoughts, and daily life activities of individuals with PDN. These results highlight the potential utility of PF components in the design and evaluation of psychological treatments for individuals suffering from PDN. The generalisability of the findings needs to be established.

Date/Venue: 4-7 September 2019, Valencia, Spain

Conference: 11th Congress of the European Pain Federation (EFIC)

Type of presentation: Poster

Abstract

A study of the role of psychological flexibility among UK adult patients with Painful Diabetic Neuropathy

Kitty Kioskli[1], Kirsty Winkley[2], Lance M McCracken[1,3]

[1] King's College London, Health Psychology Section, Psychology Department, Institute of Psychiatry Psychology and Neuroscience, London, United Kingdom

[2] King's College London, Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care, London, United Kingdom

[3] Uppsala University, Psychology Department, Uppsala, Sweden

Background and aims: Painful diabetic neuropathy (PDN) is a complex complication associated with poor glycaemic control. Current treatments for PDN aim to treat the symptoms of pain and discomfort and are mainly pharmacological but have limited effectiveness. However, less is known about alternatives such as psychological treatments and the role of psychological variables related to PDN. The aim of this study is to survey people with PDN and examine the role of psychological flexibility (PF) in relation to their daily functioning.

Methods: This is a questionnaire-based, cross-sectional study with 225 participants (mean age 52.05 $\pm$ 12.06), who were recruited from NHS and online.

Results: In correlation analyses, acceptance of pain was shown to be negatively correlated to pain intensity ($r=-0.21$, $p<0.01$), pain distress ($r=-0.25$, $p<0.01$) functional impairment ($r=-0.38$, $p<0.01$), depression severity, ($r=-0.41$, $p<0.01$), and depression impact ($r=-0.41$, $p<0.01$). Committed action also correlated negatively with functional impairment ($r=-0.22$, $p<0.01$), depression severity ($r=-0.43$, $p<0.01$) and depression impact ($r=-0.21$, $p<0.01$). Results from regression analyses show that the combination of four variables representing psychological flexibility accounted for significant variance

in most equations. In the equation for depression severity, pain intensity accounted for 23.3% of variance. In the equation for depression impact, pain intensity accounted for 13.2% of variance.

Conclusions: These results highlight the potential utility of PF in the design and implementation of psychological interventions for individuals from PDN. The reliability and generalisability of the results need to be established.

Date/Venue: 23-24 October 2019, Munich, Germany

Conference: International Conference on Controversies in Neuropathic Pain (Neuropathic-Pain2019)

Type of presentation: Oral & Poster

Abstract

A feasibility study of an online Acceptance and Commitment Therapy program for people with Painful Diabetic Neuropathy

Kitty Kioskli [1], Whitney Scott [1,3], Kirsty Winkley [2], Emma Godfrey [1], Lance M McCracken[4]

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[3] Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

[4] Uppsala University, Psychology Department, Uppsala, Sweden

Background: Painful diabetic neuropathy (PDN) is one of the most common complications of diabetes. PDN is mainly managed with medication. However, its effectiveness is limited, and most people continue to experience pain. Alternative pain management strategies are needed.

Objective: This study aimed to assess the feasibility of online Acceptance and Commitment Therapy (ACT) for people with PDN in the United Kingdom and to evaluate if a larger trial is justified.

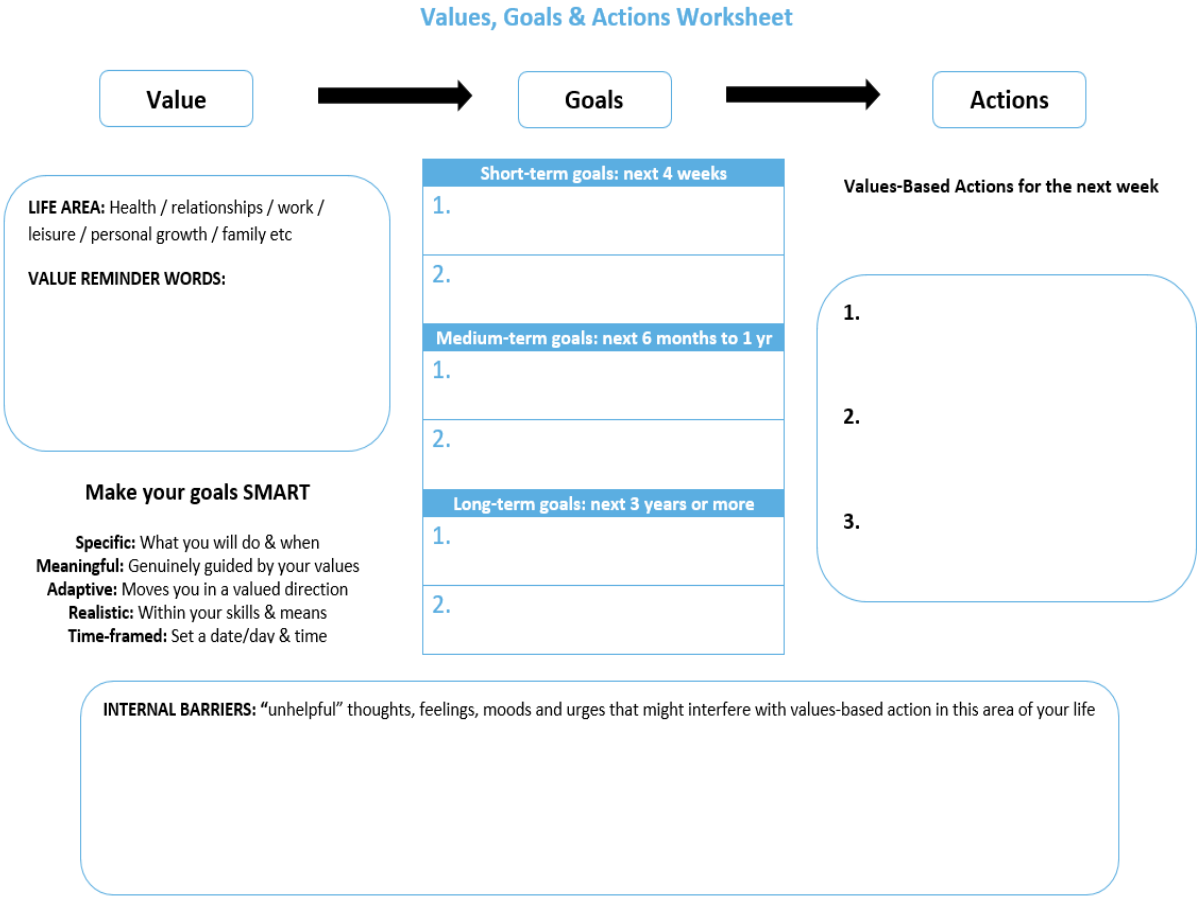
Methods: Participants were recruited online and from hospital services. This was an observational study and all participants received the online ACT program. Participants completed questionnaires at baseline and 3-month post-treatment. Primary outcomes were recruitment, treatment completion, and retention rates. Secondary outcomes were within-groups effects on pain outcomes and psychological flexibility and were evaluated via repeated measures ANOVA.

Results: From 225 potentially eligible participants, 30 took part in this study. The treatment completion rate was 40%. All participants completed 3-month questionnaires. Outcome results for the whole sample suggested that pain intensity, pain distress, cognitive fusion and self-as-context scores had a statistically significant effect for time. Treatment completers showed significantly lower levels of pain intensity, pain distress, depression symptoms and functional impairment and higher levels of committed action scores, compared to non-completers, at post-treatment. All completers reported that they felt improved after treatment.

Conclusion: Results suggest that online ACT is only acceptable to a minority of participants, as indicated by low completion rates. However, among those willing to complete it, they may achieve benefit. Refinement to increase engagement is needed.

Appendix P: ACT Worksheet Examples

Worksheet Example 1: Values Goals Actions Worksheet (Flaxman, Bond, & Livheim, 2013)



Worksheet Example 2: Open, Aware and Active Techniques (Bennett & Oliver, 2019)

OPEN

Learning to respond more effectively to the painful and unpleasant thoughts and feelings that are an inevitable part of the human experience

Open techniques:

Acceptance (e.g. 'finger traps' or 'tug of war' metaphors)

Defusion (e.g. Magritte's 'Human Condition' painting)

Discriminating between self and self-stories (e.g. 'sky and the weather', 'pizza', or 'chessboard' metaphors, 'Big I – little I' technique)

AWARE

Easing out of automatic pilot and contacting what is going on around us right here right now

Aware techniques:

Mindfulness (promoting the use of formal and/or informal mindfulness practice to improve 'noticing')

Techniques that set up and promote an observer perspective (e.g. 'The Matrix')

Perspective taking exercises (e.g. seeing this from someone else's eyes, seeing this from another time)

Promoting any skills in observing, describing, and tracking one's own internal experience

ACTIVE

Becoming clear on what matters and pursuing those things vigorously. Living life purposefully.

Active techniques:

Values clarification (e.g. What would 'the chooser' choose? What matters? What do you want to stand for in life?)

Choosing kindness and self-compassion (e.g. What would a kinder response look like?

Turning values into action (e.g. formulating value-driven behavioural goals, working out the specific actions associated with them, discussing what internal barriers might show up)

Pain Medicine, 0(0), 2019, 1–18
doi: 10.1093/pm/pnz071
Review Article

Psychosocial Factors in Painful Diabetic Neuropathy: A Systematic Review of Treatment Trials and Survey Studies

Kitty Kioskli, MSc,* Whitney Scott, PhD,*,† Kirsty Winkley, PhD,‡ Stavros Kylakos, MSc,§ and Lance M. McCracken, PhD*,†,¶

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Funding sources: This study was funded through a PhD fellowship grant awarded by Diabetes UK. Also, this research is independent work supported by the National Institute for Health Research (NIHR; Postdoctoral Fellowship, Dr. Whitney Scott, PDF-2015–08-059). Professor Lance McCracken was partly funded through the Biomedical Research Centre at South London and Maudsley National Health Service (NHS) Foundation Trust and King's College London.

Disclaimer: The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health.

Conflicts of interest: None declared.

Abstract

Objective. Diabetes mellitus is associated with a number of complications that can adversely impact patients' quality of life. A common and often painful complication is painful diabetic neuropathy. The aims of this study were to systematically review and summarize evidence from studies of psychological treatments and psychosocial factors related to painful diabetic neuropathy and assess the methodological quality of these studies. **Methods.** Electronic databases, related reviews, and associated reference lists were searched. Summaries of participants' data relating to the efficacy of psychological treatments and/or to associations between psychosocial factors and outcomes in painful diabetic neuropathy were extracted from the included studies. The methodological quality of included studies was assessed using two standardized quality assessment tools. **Results.** From 2,921 potentially relevant titles identified, 27 studies were included in this systematic review. The evidence suggests that depression, anxiety, sleep, and quality of life are the most studied variables in relation to pain outcomes in painful diabetic neuropathy and are consistently associated with pain intensity. The magnitude of the associations ranged from small to large. **Conclusions.** Research into psychosocial factors in painful diabetic neuropathy is unexpectedly limited. The available evidence is inconsistent and leaves a number of questions unanswered, particularly with respect to causal associations between variables. The evidence reviewed indicates that depression, anxiety, low quality of life, and poor sleep are associated with pain in painful diabetic neuropathy. The disproportionate lack of research into psychological treatments for painful diabetic neuropathy represents a significant opportunity for future research.

Key Words: Painful Diabetic Neuropathy; Psychological Interventions; Psychosocial Factors; Systematic Review

Introduction

Diabetes mellitus (DM) is highly prevalent and a significant public health problem [1]. Common complications of DM include cerebrovascular and cardiac diseases, kidney failure, stroke, foot ulcer, blindness, and amputation [2,3]. Another frequent complication of DM is painful diabetic neuropathy (PDN), which affects 25–30% of people with DM [3–5].

PDN diagnosis is a clinical one and is based on the patient's description of pain, which is often described as a prickling, burning, deep aching, or sharp sensation, similar to an electric shock [6]. Subjective report of these painful symptoms can be used to screen for possible PDN; however, definitive diagnosis requires the presence of objective PDN signs (e.g., decreased ankle reflex) and findings confirming nerve dysfunction, such as using nerve conduction or through skin biopsy. Although these objective indicators are required to confirm PDN diagnosis, for practical reasons, some studies rely on self-reported neuropathic pain symptoms for people with diabetes as an indicator of possible PDN [4].

PDN primarily involves the toes, feet, and legs and is associated with significant interference with mobility, sleep, mood, social interactions, and overall quality of life (QOL) [7–9]. PDN appears to significantly impact mental health, including anxiety and depression [10,11], which in turn contributes to poorer outcomes overall [12]. Essentially, PDN is a chronic disease associated with long-term suffering and disability for many people [13,14].

At present, most treatments for neuropathic pain are pharmacological [15–17]. The American Diabetes Association (ADA), recommends optimization of glucose control to achieve the prevention or delay of PDN, as well as pregabalin or duloxetine as pharmacological options for pain management [18]. However, no single treatment has proven effective enough for pain relief or prevention [19]. Findings are similar in the broader neuropathic pain literature. A systematic review of published and unpublished studies from 174 randomized controlled clinical trials (RCTs) [20] and a meta-analysis of 229 RCTs [21] examined the medical management of neuropathic pain. The meta-analysis found that outcomes from trials were modest, including a number needed to treat (NNT; ≥50% relief) of 6.4 (95% confidence interval [CI] = 5.2–8.4) for duloxetine, 7.7 (95% CI = 6.5–9.4) for pregabalin, 7.7 (95% CI = 6.5–9.4) for gabapentin, and 10.6 (95% CI = 7.4–19.0) for capsaicin patches. According to these results, even when PDN is treated with medication, many people continue to experience significant pain. These results suggest a need for new or additional treatments, potentially including nonpharmacological interventions.

Within the broader chronic pain literature, there is good evidence supporting psychological treatments, such as cognitive behavioral therapy (CBT), for chronic pain [22–24]. However, it appears that there are limited published studies of psychological treatments for people with diabetic neuropathies [25,26] and only one literature review examining physical and psychological interventions for people with PDN [8]. This earlier review searched the literature up to July 2014 and identified only two psychological intervention studies. An updated review on this important topic appears due. Also, it is unknown which psychosocial factors might impact outcomes in people with PDN from a wider range of study designs. A wider view of psychosocial factors could prove fruitful, as it could lead to treatment developments that have not yet been conceived.

The purpose of this study was to synthesize and evaluate the evidence from trials of psychological treatments for PDN and other research into psychosocial factors in relation to PDN outcomes. From this we intended to 1) identify current psychological interventions for individuals who suffer from PDN and examine their effectiveness, 2) identify potentially modifiable psychosocial factors that might influence clinical outcomes associated to PDN, and 3) assess the methodological quality of the included studies.

Methods

Registration

This systematic review protocol is registered with PROSPERO (registration number CRD42017060339) and may be accessed online at:https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017060339.

The current review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [27] and established guidelines for narrative synthesis [28].

Search Strategy

We searched the following electronic databases from 1946 to August 10, 2018: Medline, Embase, PsycINFO, Cinahl, Web of Science, ISRCTN registry, ClinicalTrials.gov registry, and EU Clinical Trials registry. Also, the reference lists of all included papers and related published reviews [29] were screened to identify any additional eligible studies. The PICOS framework was used to develop the search strategy explicitly for the treatment trials. Our target population was patients suffering from neuropathic pain due to diabetes. Included interventions were any study involving psychological treatments. In addition to treatment trials, observational studies examining relationships between psychosocial factors and relevant outcome variables were also sought. All comparators were eligible. The selected outcomes were physical and emotional functioning, pain experience, pain-related interference with functioning, or QOL (Table 1).

Furthermore, the MeSH and free-text terms were divided into three groups—PDN, psychological interventions, and psychosocial factors—including all study designs, in order to identify both observational studies and RCTs (Supplementary Data). Particularly, the boolean operator "OR" was used to enable identification of either relevant RCTs *or* observational designs measuring psychosocial factors in relation to pain outcomes in PDN.

Table 1. PICOS Inclusion/Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Population	Adults (minimum age 18 years) & clear diagnosis of PDN	Children, adolescents (under 18 years), & neuropathic pain due to other causes
Intervention	Any psychological treatment addressing psychosocial factors *or* studies measuring psychosocial factors for PDN and allowing the examination of these in relation to pain outcomes	Interventions that are only educational
Control	All comparators are eligible for this systematic review	–
Outcomes	Physical functioning Emotional functioning Pain experience Pain related interference Symptoms and adverse effects Quality of life	–
Study design	Any	Reviews
Publication type	Published full-text articles	Unpublished dissertations and articles, editorials, letters/ uncompleted trials
Language	English	Non-English articles

– = not applicable; PDN = painful diabetic neuropathy.

Inclusion and Exclusion Criteria

We included any study involving psychological treatments incorporating any of the outcomes specified: physical or emotional functioning, pain experience, pain-related interference, or QOL in individuals with PDN. Also, we included studies designed to investigate the association between psychosocial factors, for instance, emotional responses, thoughts, beliefs, cognitive factors, or other behavioral patterns, and the designated pain outcomes. Studies examining potentially modifiable social processes, such as perceived quality of social support, in relation to pain outcomes were also included. Studies were excluded if they were not written in English or were not published as a full-text article. Additionally, studies that only investigated pain prevalence, and not the association between pain outcomes and psychosocial factors, were not eligible. Studies that assessed only unmodifiable sociodemographics (e.g., ethnicity) in relation to pain outcomes were excluded. Studies were also excluded if they were solely educational interventions (meaning primarily focused on enhancing knowledge or providing information, rather than more active processes of psychological or behavioral change). Participants within the included studies were adults, aged 18 years and older (at the time of their entry into the study), with a stated diagnosis of PDN. Studies of participants who suffered from neuropathic pain due to causes other than diabetes were not included.

Screening of Studies

After running searches in each electronic database, the predefined inclusion criteria were applied independently by two reviewers (KK, SK) in order to screen all potentially relevant titles and abstracts. After screening titles and abstracts for eligibility, the remaining potentially eligible full-text articles were reviewed for selection. Disagreements regarding eligibility were discussed, where required, so that a consensus was reached. Disagreements that could not be resolved through discussion were settled by input from a third reviewer (LM, KW, or WS).

Data Extraction

The data extraction tool included the following: publication date, authors, country, journal, study design, types of interventions or psychosocial factors investigated, pain and related outcomes, participants' characteristics, study setting, study inclusion and exclusion criteria, recruitment method, reported medications, duration of PDN, outcome measures used, and statistical analyses. The data were extracted from the eligible studies by three reviewers (KK, SK, or WS). KK extracted data from all studies, whereas SK and WS each independently extracted data from approximately half of the studies. If the reviewers failed to reach a consensus on the extracted data, a third opinion was provided by another member of the research team (LM or KW).

Quality Assessment

The methodological quality of the included studies was evaluated using the Downs and Black quality assessment tool [30] for observational studies or the Cochrane risk of bias tool for RCTs [31], depending on the design of the study.

The Downs and Black quality assessment tool [30] has been identified as appropriate for quality assessment in systematic reviews. It was applied to nonrandomized trials and other observational studies. The checklist was modified minimally to meet the needs of the current systematic review. The methodological quality tool contained 27 items. The component ratings are divided as follows: A: Reporting, Score 0–10 (eight questions); B: External Validity, Score 0–3 (three questions); C: Internal Validity–Bias, Score 0–7 (seven questions); D: Internal Validity–Confounding, Score 0–7 (seven questions).

The Cochrane risk of bias tool [31] is a widely used tool for assessing bias and flaws in the conduct, design, analysis, and reporting of RCTs and is better suited to this than the Downs and Black tool [30]. This risk of bias assessment tool includes selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.

The checklists were administered by three independent reviewers (KK, SK, or WS) and cross-checked for

consistency. Again, KK assessed all the studies, and SK and WS each assessed half of the studies. Any disagreements were resolved by a third reviewer (LM or KW).

Data Analysis and Data Synthesis

Most studies investigated associations between more than one psychosocial variable and pain outcomes. The reported results are organized according to the specific psychosocial factors and pain outcomes included in the studies. The magnitude of relations from correlational methods was reported in terms of the correlation coefficient *r* when available.

Cohen's *d* was calculated by the first author (KK) to reflect effect sizes for between-group comparisons, based on the means and SDs reported in each study. For variables that were assessed by more than one measure, a Cohen's *d* was calculated for each measure, and the final effect size reported for the variable was the mean of the Cohen's d of all measures [32,33]. The calculated *d*s are interpreted, according to Cohen, as small ($d = 0.2$), medium ($d = 0.5$), or large ($d = 0.8$).

Ninety-five percent confidence intervals were calculated for Cohen's *d* and correlation coefficient *r* (for studies that reported a within-group correlation coefficient). For Cohen's *d*, the 95% CI was calculated by first identifying the t-value and then using the "ci.smd" function of the MBESS package in R [34]. The t-value was calculated as follows [35]:

$$t = Cohen's\ d\ \times \sqrt{\frac{Sample\ Size\ 1 \times\ Sample\ Size\ 2}{Sample\ Size\ 1 + Sample\ Size\ 2}}$$

. For the correlation coefficient *r*, the 95% CI was calculated by first transforming the *r* to z', calculating the standard error for z', the 95% CI for z', and then transforming it back to values for *r*. The correlation coefficient *r* was transformed to z' with the following formula [36]:

$$z' = 0.5 \times [ln(1 + r) - ln(1 - r).]$$

The standard error for z' was calculated by:

$$SE = \frac{1}{\sqrt{Sample\ Size - 3.}}$$

The lower and upper bounds of the 95% CI for z' were found as follows:

$$Lower\ Bound = z' - 1.96\ \times SE;$$

$$Upper\ Bound = z' + 1.96\ \times SE.$$

Finally, the lower and upper bound values were transformed back to *r* values using the equation originally used to transform *r* to z'.

Results

Study Selection

The detailed selection process for included studies can be found in Figure 1. Each database was searched individually, and the total number of hits was 2,922; 2,226 articles remained after deduplication. After applying the predefined inclusion and exclusion criteria to the titles and abstracts, 41 articles remained for full-text review by the two reviewers. The manual search of the reference lists revealed seven more studies that did not appear during the electronic searches. At the end of the screening and selection process, 27 studies (29 published papers) met criteria and were included in this systematic review.

General Study Characteristics

The 27 studies found eligible for this systematic review were published between 1998 [37] and 2018 [38]. The majority of the studies (17/27) were cross-sectional [3,6,9–12,38–52]. Two studies were described as case–control [37,53], three as prospective cohort designs [4,14,54], and three were RCTs [25,26,55].

Most of the studies recruited participants from the United States (10 studies, 37%), the UK (six studies, 22%), and the Netherlands (two studies, 8%). The remaining studies (nine studies, 33%), recruited participants from a range of countries across Europe, Asia, and North and South America. The mean ages ±SDs of participants reported in the studies ranged from 45.9 ± 15 to 74.6 ± 10.8 years. Twenty-six out of the 27 studies included both male and female participants, while one included only male participants [26]. Detailed information regarding study characteristics can be found in Table 2 and the Supplementary Data.

Clinical Characteristics of the Studies

Regarding the participants' clinical characteristics, 40.9% to 88.3% of the participants were taking medications for PDN. The most common medication types reported within the studies were tricyclic antidepressants (33.5%), nonsteroidal anti-inflammatory drugs (26.8%), anticonvulsants (26.1%), and opioids (13.6%) [9–12,37,40,42–45,47–50]. Approximately 60% of the included studies did not report participants' use of pain medication.

Comorbid conditions were typically reported by 80% of participants in the included studies. The most commonly reported conditions were congestive heart failure, hypertension, nephropathy, foot ulcer, dyslipidemia, retinopathy, and fibromyalgia [3,9–12,37,38,40,42–45,47,48]. Fifty percent of the studies did not report participants' comorbidities.

PDN duration was not consistently reported. However, 11 studies included reports of participants' time since PDN diagnosis [4,6,12,14,25,39,42,43,45,46,48]. From the studies providing data, the PDN duration ranged from 2.4 to 7.8 years. Forty-four percent (12/27) of the studies did not report time since diagnosis (Table 2).

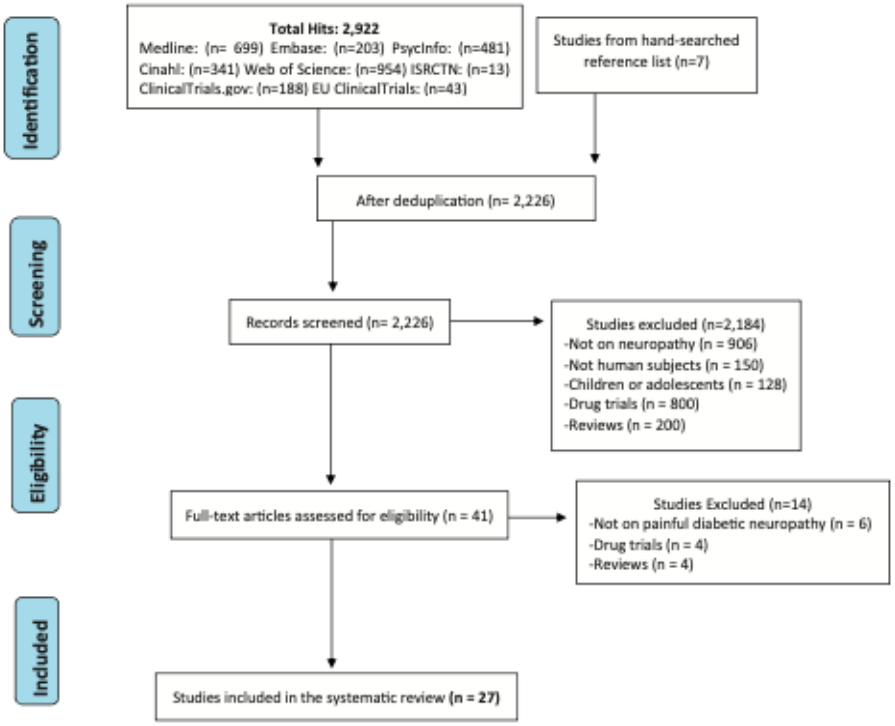

Figure 1. Flowchart: Selection process.

Treatment Outcomes

Three out of the 27 studies were RCTs of psychological treatments for patients suffering from diabetic neuropathies (Table 3) [25,26,55].

Teixeira conducted a pilot trial of mindfulness meditation for PDN [25]. The intervention group (n = 10) received training in mindfulness, and the control group (n = 10) received an "attention-placebo" treatment for four weeks. The results indicated a small effect in the mindfulness group compared with the control on QOL. It was also found that pain and poor sleep were positively correlated in the full sample.

Pfmmater conducted a study of thermal biofeedback for PDN [55]. The experimental group (n = 10) received six sessions of thermal biofeedback, and the control group (n = 11) six sessions with a therapist talking about nonstressful topics. Overall, this study did not produce any statistically significant effects between the experimental and control groups, or any other consistent associations. Notably, 11 out of the 21 participants withdrew from the study.

Lastly, Otis et al. investigated CBT for PDN (n = 11) compared with treatment as usual (TAU) (n = 8) [26]. Results indicated that participants in the CBT group improved on pain severity and interference compared with the TAU group at four-month follow-up, but there was no improvement on depressive symptoms for either group. Results suggested large between-group effects in pain severity and interference, both at post-treatment and follow-up. For depression, medium and small between-group effects were observed at post-treatment and follow-up, respectively.

Depression and Pain Outcomes

Eight cross-sectional studies [3,10,12,43,45,48–50] investigated the role of depression in relation to pain in PDN (Table 4). Two studies investigated the association between depression and pain outcomes and reported large positive effect sizes [3,41]; one reported medium [48], and another small (Table 4) [10].

One study found that depression and pain severity are positively but weakly associated. This was a cross-sectional study that did a group comparison in three regions (Asia, Latin America, Middle East) [43].

Three studies investigated depression in relation to pain, but data (means and SDs) were not available to compute the effect sizes. One study [45] reported that participants with chronic pain with neuropathic characteristics had higher depression scores than participants without neuropathic pain. One study [49] reported a significant difference in depression between participants

Table 2. Studies' general characteristics

Study	Design	Location	Recruitment Sites	Sample Size (N) per Group	Mean Age, y	Male/Female, %	PDN Duration
AL-Mahmood et al. (2018) [51]	Cross-Sectional	Malaysia	Medical Outpatient Department Clinic of Hospital (MOPD) clinic of hospital Tegku Ampaun Afzan (HTAA)	T: 90	65	60/40	–
Benbow et al. (1998) [37]	Case–control	UK	Adult hospital, diabetic clinic	T: 116, PDN: 41, DM: 38, C: 37	55.6	70/30	–
Bouhassira et al. (2013) [45]	Cross-sectional	France	Hospital departments, private practice	T: 766, PDN: 156, T1DM: 297, T2DM: 469	48.3	55/45	At least 1 y at 57.4% of the participants
Currie et al. (2006) [40]	Cross-sectional	UK	Hospital Trust	T: 1125, T1DM: 236, T2DM: 889	64	56/44	–
Dobrota et al. (2014) [3]	Cross-sectional	Croatia	Clinical hospital, university clinic for diabetes	T: 160, PDN: 80, DM: 80	62.4	52/48	–
Galer et al. (2000) [4]	Prospective cohort	USA	Advertisements, newsletters, letters to physicians	T: 105	62.9	50/50	(diagnosed at 56.7 y of age)[SC]
Geelen et al. (2016, 2017) [9, 11]	Cross-sectional	Netherlands	Informative letter to regional hospital	T: 154	65.7	62/38	–
Gore et al. (2005, 2006) [12, 41]	Cross-sectional	USA	Primary care	T: 255	61.3	49/51	6.4 y
Hoffman et al. (2009) [43]	Cross-sectional	Asia, Latin America, Middle East	Investigational centers	T: 401	57.3	38/62	2.73 y
Jacovides et al. (2014) [47]	Cross-sectional	South Africa	Public and private outpatient clinics	T: 961, PDN: 291, DM: 670	55.9	51/49	–
Kulkantrakorn et al. (2013) [6]	Cross-sectional	Thailand	Internal medicine and neurology clinic at a university hospital	T: 33	60.5	46/54	4 y
Levterova et al. (2018) [38]	Cross-sectional	Bulgaria	University hospital "Kaspela," Plovdiv	T: 37	58.3	57/43	–
Lewko et al. (2007) [53]	Case–control	Poland	Endocrinology, Diabetes and Internal Medicine clinics at the Medical University of Bialystok	T: 59, PDN: 22, DM: 37	61.3	18/32	–
Mai et al. (2015) [14]	Prospective-observational	Canada	The Canadian Neuropathic Pain Database	T: 60	57.1	57/43	4.9 y
Otis et al. (2013) [26]	Single-blind, RCT	USA	Advertisements in the Dept. of Veterans Affairs medical center	T: 19, CBT: 11, C: 8	63	100/0	–
Pfmmater (2012) [55]	RCT	USA	Databases/advertisements/posters	T: 21, BF: 10, C: 11	59.3	53/47	–
Sadosky et al. (2013) [46]	Cross-sectional	USA	Community-based physician practices	T: 112	61.1	47/53	5.9 y
Selvarajah et al. (2014) [48]	Cross-sectional	UK	Multidisciplinary outpatient service	T: 142	61.2	57/43	8.4 y
Teixeira (2010) [25]	Open label, RCT	USA	Medical practices and retirement communities	T: 20	74.6	25/75	7.76 y

(continued)

Table 2. continued

Study	Design	Location	Recruitment Sites	Sample Size (N) per Group	Mean Age, y	Male/Female, %	PDN Duration
Themistocleous et al. (2016) [49]	Cross-sectional	UK	Primary care practices, diabetes clinics, teaching hospitals, neurology clinics, advertisements	T: 191, No PDN: 80, Mild PDN: 41, Moderate/Severe PDN: 70	67.23	45/55	–
Tölle et al. (2006) [42]	Cross-sectional	France, Germany, Italy, Netherlands, Spain, UK	Community-based practices	T: 140	65.6	58/42	3–6 m: 14% 7–12 m: 22% 13–35 m: 43% ≥36 m: 61% [SC]
Van Acker et al. (2009) [44]	Cross-sectional	Belgium	Outpatients diabetes clinics	T: 1111, PDN: 478, T1DM: 344, T2DM: 767	T1DM: 45.9, T2DM: 63.6	T1DM: 54/46 T2DM: 57/43	–
Vileikyte et al. (2005) [10]	Cross-sectional	UK, USA	–	T: 484	61.86	70/30	–
Vileikyte et al. (2009) [54]	Prospective cohort	UK, USA	–	T: 495	61.24	71/29	–
Wickramasinghe et al. (2016) [50]	Cross-sectional	Sri Lanka	Diabetic clinic	T: 235	56	35/65	–
Zelman et al. (2005) [39]	Cross-sectional	USA	Primary care	T: 255	61.3	45/51	6.4 y
Zelman et al. (2006) [52]	Cross-sectional	USA	Primary care	T: 255	61.3	45/51	6.4 y

Location: At the time, the location is provided to the lowest level reported (i.e., city). Recruitment sites: Where the recruitment site is not reported, recruitment methods are. Sample size: Sample sizes are provided in groups where given by the authors. Mean age: Where the mean age is not reported, the alternative is. Only totals are reported. Male/female: Only totals are reported. Where the % doesn't add up to 100, it means that there are missing data. PDN duration: Most values are given as mean ± SD. SC: Galer provides the mean age when PDN was diagnosed for the sample; Tolle presents the duration of PDN in ranges of months and percentage of total sample falling within each range (special case).

– = not reported; BF = biofeedback; C = control group; CBT = cognitive behavioural therapy; DM = diabetes mellitus; PDN = painful diabetic neuropathy; RCT = randomized controlled trial; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; T = total.

Table 3. Outcomes associated with RCTs of psychological interventions

Study	Intervention outcome/ Psychosocial variable	Comparison	Cohen's *d* (95% CI)	Correlation *r* (95% CI)	Magnitude Interpretation	*P* Value
Otis et al. (2013) [26]	CBT (post-treatment) - Depression	Between-group	0.68 (–0.19 to 1.55)	–	Medium	>0.05
	CBT (follow-up) - Depression	Between-group	0.47 (–0.39 to 1.33)	–	Small	>0.05
	CBT (post-treatment) - Pain Interference	Between-group	0.91 (0.02 to 1.8)	–	Large	>0.05
	CBT (follow-up) - Pain Interference	Between-group	0.85 (–0.03 to 1.74)	–	Large	>0.05
	CBT (post-treatment) - Pain Severity	Between-group	0.88 (–0.01 to 1.77)	–	Large	>0.05
	CBT (follow-up) - Pain Severity	Between-group	0.83 (–0.05 to 1.71)	–	Large	>0.05
Teixeira (2010) [25]	Mindfulness - QOL	Between-group	–0.16 (–1.1 to 0.78)	–	Small	>0.05
	QoL and Sleep	Whole sample	–	0.53 (0.048 to 0.813)	Large	<0.05
Pfmmater (2012) [55]	TB - Pain Severity/ Control (Session 1)	Whole sample	–	–0.42 (–0.721 to 0.014)	Large	>0.05
	TB - Pain Severity/ Control (Session 4)	Whole sample	–	–0.62 (–0.830 to –0.257)	Large	<0.05
	TB - Pain Severity/ Control (Session 6)	Whole sample	–	–0.65 (–0.845 to – 0.303)	Large	<0.01

– = not applicable; CI = confidence interval; Correlation r = correlation coefficient; QOL = Quality Of Life; RCT = randomized controlled trial; TB: thermal biofeedback.

suffering from moderate/severe neuropathic pain and participants with no/mild neuropathic pain; one study [50] found that depression among DPN participants was higher than in those without DPN.

Anxiety and Pain Outcomes

Five cross-sectional studies investigated anxiety in relation to pain severity and pain interference (Table 4) [12,43,45,48,49]. One study [48] investigated the association between anxiety and pain in patients with confirmed PDN differing in pain intensity and found a medium effect size, and one study [12] found a large effect size between patients with mild and severe PDN. However, contrary to this, another study [43] demonstrated an overall weak and negative effect size between anxiety and pain severity. This appeared to be due to unexpectedly high anxiety reported in some of their low-pain participants; otherwise the trend was for those reporting severe pain to also report higher anxiety.

Two further studies also investigated anxiety in relation to pain outcomes, but data were not available to compute the effect sizes. One study [45] reported that participants with chronic pain and neuropathic characteristics had higher anxiety scores compared with those without neuropathic pain, and one study [49] investigated pain-related anxiety and found that participants with moderate/severe neuropathy reported significantly higher scores compared with participants with mild/no neuropathy.

Sleep and Pain Outcomes

Seven cross-sectional studies examined the association between sleep and pain in PDN (Table 4) [12,43,45,47,48,50,52]. Two studies reported large effect sizes. In the first study, participants were grouped according to pain severity, and a strong association between pain severity and sleep impairment was found [12]. These findings were supported by a more recent study that reported a large effect between pain and sleep interference [47]. One study found a medium effect when comparing individuals with PDN and the general US population, whereas another study [43] found a small effect between sleep and pain.

Three studies also investigated the relation between sleep disturbances and pain, but data were not available to compute the effect sizes. One study [45] reported that participants with neuropathic pain had more sleep disturbance than participants without neuropathic pain. One study [49] showed significantly greater sleep impairment in participants with moderate/severe neuropathy relative to those with mild/no neuropathy. One study [50] concluded that 43.7% of the total sample had sleep disturbances due to their neuropathic symptoms.

Catastrophic Thinking and Pain Outcomes

Two cross-sectional studies [48,49] and one prospective cohort [14] examined pain catastrophizing (Table 4). It is worth noting that there are three dimensions within catastrophizing: rumination, magnification, and helplessness [56]. One study showed that helplessness and rumination are strongly associated with the experience of pain in

Table 4. Associations between depression, anxiety, QOL, sleep, and pain outcomes for studies reporting sufficient data to compute effect sizes

Study	Comparison	Study Design	Type of Analysis*	Pain/Neuropathy Outcome (Assessment)	Psychosocial Assessment	Cohen's *d* (95% CI)	Correlation *r* (95% CI)or *β* if Only Multivariate Regression Reported	Magnitude of Relation/ Effect	*P* Value	Proportion of Significance
Depression										
Dobrota et al. (2014) [3]	Between-group	Cross-sectional	Univariate	Presence of Pain (VAS, LANSS)	BDI	1.07 (0.73 to 1.4)	–	Large	<0.001	–
Gore et al. (2005, 2006) [12, 41]	Between-group	Cross-sectional	Univariate	Pain Severity (BPI)	HADS-D	0.99 (0.66 to 1.32)	–	Large	<0.001	–
Hoffman et al. (2009) [43]	Between-group	Cross-sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	HADS-D	0.02 (–0.51 to 0.55)	–	Weak	N/R	1/3
Selvarajah et al. (2014) [48]	Within-group	Cross-sectional	Multivariate (reported *r* is univariate)	Pain Intensity (NPS)	HADS-D	–	0.33 (0.161 to 0.480)	Medium	<0.01	–
Vileikyte et al. (2005) [10]	Within-group	Cross-sectional	Multivariate	Pain Severity (NeuroQoL)	HADS-D	–	Pain predicting depression $\beta = -0.27$ (0.185 to 0.351)	Small	<0.001	–
Vileikyte et al. (2009) [54]	Baseline/follow-up	Longitudinal (change in pain predicting follow-up depression)	Multivariate	Pain Severity (NeuroQoL)	HADS-D	–	Pain intensity predicting depression $\beta = -0.04$ (–0.146 to 0.067) Pain disability predicting depression $\beta = 0.16$ (0.054 to 0.262)	Weak	< 0.05 <0.01	–
Anxiety										
Gore et al. (2005, 2006) [12, 41]	Between-group	Cross-sectional	Univariate	Pain Severity (BPI)	HADS-A	0.97 (0.64 to 1.29)	–	Large	<0.001	–
Hoffman et al. (2009) [43]	Between-group	Cross-sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	HADS-A	–0.15 (–0.68 to 0.18)	–	Weak	N/R	2/3
Selvarajah et al. (2014) [48]	Within-group	Cross-sectional	Multivariate (reported *r* is from univariate analysis)	Pain Intensity (NPS)	HADS-A	–	0.45 (0.295 to 0.582)	Medium	<0.01	–
Pain/Diabetes-Related Fears										
Geelen et al. (2017) [11]	Within-group	Cross-sectional	Multivariate	Pain Severity and Disability (VAS, PDI)	HFS, TSK, PASS-20, FES-I, TSF, BFNE	–	0.78† (0.695 to 0.839) 0.73† (0.635 to 0.796)	Large	N/R	3/11

(continued)

Table 4. continued

Study	Comparison	Study Design	Type of Analysis*	Pain/Neuropathy Outcome (Assessment)	Psychosocial Assessment	Cohen's *d* (95% CI)	Correlation *r* (95% CI) or *β* if Only Multivariate Regression Reported	Magnitude of Relation/ Effect	*P* Value	Proportion of Significance
Quality of Life										
Dobrota et al. (2014) [3]	Between-group	Cross-sectional	Univariate	Pain Presence (VAS, LANSS)	SF-36	−1.12 (−1.45 to −0.78)	–	Large	<0.001	–
Geelen et al. (2017) [11]	Within-group	Cross-sectional	Multivariate (reported *r* is from univariate analysis)	Pain Severity and Disability (VAS, PDI)	QOL-DN	–	0.49 (0.348 to 0.610)	Large	<0.01	–
Gore et al. (2005, 2006) [12, 41]	Between-group	Cross-sectional	Univariate	Pain Severity (BPI)	EQ-5D	−1.96 (−2.34 to −1.58)	–	Large	<0.01	–
Hoffman et al. (2009) [43]	Between-group	Cross-sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	EQ-5D VAS	−0.12 (−0.64 to 0.41)	–	Small	<0.05	–
Jacovides et al. (2014) [47]	Between-group	Cross-sectional	Univariate	Pain Presence (DN4)	EQ-5D	−0.95 (−1.1 to −0.81)	–	Large	N/R	–
Levterova et al. (2018) [38]	Between-group	Cross-sectional	Univariate	Pain Presence (DN4)	SF-36v2	−0.5 (−2.13 to 1.13)	–	Medium	N/R	4/8
Lewko et al. (2007) [53]	Within-group	Cross-sectional case–control	Univariate	Presence of diabetic peripheral neuropathy (assessment of neuropathy unclear)	SF-36v2, AIS	–	0.48 (0.256 to 0.656)	Large	<0.05	–
Sadosky et al. (2013) [46]	Between-group	Cross-sectional	Univariate	Pain Severity (BPI-SF)	SF-12v2	−1.49 (−2.11 to −0.86)	–	Large	<0.001	–
Zelman et al. (2005) [39]	Between-group	Cross-sectional	Univariate	Severity (BPI, VRS)	EQ-5D	−15.69 (−17.44 to −13.89)	–	Large	<0.001	–
Zelman et al. (2005) [39]	Between-group	Cross-sectional	Univariate	Severity (BPI, VRS)	SF-12v2	−1.09 (−1.42 to 0.76)	–	Large	<0.001	–
Sleep										
Gore et al. (2005, 2006) [12, 41]	Between-group	Cross-sectional	Univariate	Pain Severity (BPI)	MOS	1.46 (1.11 to 1.8)	–	Large	<0.001	–
Hoffman et al. (2009) [43]	Between-group	Cross-sectional (baseline data from an RCT of analgesic medication)	Univariate	Pain Severity (mBPI-SF)	MOS	0.31 (−0.22 to 0.84)	–	Small	<0.05	–
Jacovides et al. (2014) [47]	Between-group	Cross-sectional	Univariate	Pain Presence (DN4)	DSIS	1.12 (0.98 to 1.27)	–	Large	N/R	–

(continued)

Table 4. continued

Study	Comparison	Study Design	Type of Analysis*	Pain/Neuropathy Outcome (Assessment)	Psychosocial Assessment	Cohen's *d* (95% CI)	Correlation *r* (95% CI) or β if Only Multivariate Regression Reported	Magnitude of Relation/ Effect	*P* Value	Proportion of Significance
Zelman et al. (2006) [52]	Between-group (Cohen's *d*)/ within group (β)	Cross-sectional	Multivariate	Severity (BPI-DN)	MOS	0.47 (0.33 to 0.61)	Pain predicting sleep problems: $\beta = 0.30$ (0.184 to 0.408)	Medium	<0.001	–

Only groups of absolute interest are reported in this table. *P* values: In instances where an effect size is calculated for a number of different subscales with different *P* values, a proportion of significance is reported as the number of comparisons of the total comparisons that reported a significant difference. For papers that had three or more groups based on pain severity, a comparison was undertaken between the groups with the least severe symptoms and the most severe symptoms.

– = not applicable; AIS = Acceptance of Illness Scale; BDI = Beck Depression Inventory; BFNE = Brief Fear of Negative Evaluation Scale; CI = confidence interval; DN4 = Douleur Neuropathique 4; DSIS = Daily Sleep Interference Scale; EQ-5D = EuroQOL; FES-I = Falls Efficacy Scale-International; HADS = Hospital Anxiety and Depression scale; HFS = Hypoglycaemia Fear Survey; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; mBPI = modified Brief Pain Inventory; MOS = Medical Outcomes Study–Sleep scale; MPQ = McGill Pain Questionnaire; NDS = Neuropathy Disability Score; NPS = Neuropathic Pain Scale; NeuroQol = Neuropathy and Foot Ulcer–specific Quality of Life Instrument; N/R = not reported; PASS-20 = Pain Anxiety Symptom Scale; PDI = Pain Disability Index; QOL-DN = Norfolk Quality of Life Questionnaire; *r* = correlation coefficient effect size or otherwise explained in the comments; SF-12v2 = Short Form Health Survey Version 2; SF-36 = Short Form Health Survey; TSF = Tampa Scale of Fear of Fatigue; TSK = Tampa Scale of Kinesiophobia; VAS = visual analog scale; VRS = verbal rating scale.

*When both univariate and multivariate analyses were reported in the same paper, we extracted univariate data, given differences in multivariate models across studies that limit their interpretability. For cases in which only a multivariate model was reported, those data were extracted.

†The effect size reported was not originally calculated by the author of the study but by the first author of this systematic review.

diabetic neuropathy [48]. In another study, participants with moderate/severe PDN scored significantly higher on catastrophizing than those with no/mild PDN [49]. Finally, in one study catastrophizing did not predict outcome, possibly because the sample size was relatively small (n = 60) [14]. None of the studies described provided adequate data to compute effect sizes.

Other Psychosocial Variables and Pain Outcomes

One study investigated the association between acceptance of illness and QOL, finding a large effect size (Table 4) [53]. One study, of prospective cohort design, investigated depression as an outcome variable at 18 months and found that this was predicted by increased pain from baseline to nine months [54]. Another study investigated the association between acceptance of pain and anxiety and depression. The results demonstrated that lower acceptance scores were strongly associated with higher levels of depressive symptoms and anxiety. However, the data were insufficient to calculate an effect size [48].

One study investigated the role of a number of different fears, including fear of movement (kinesiophobia), fear of fatigue, fear of hypoglycemia, fear of pain, fear of falling, and fear of negative evaluation in relation to QOL. This study found medium to large correlations between QoL and these fear-related variables (range: $r = 0.39$–0.71). This study also found medium to large correlations between fear-related variables and disability (range: $r = 0.28$–0.66) [9].

Pain and Quality of Life

Most of the studies included in this review (20/27) aimed to capture the perceived impact of PDN on QOL (Table 4). These studies were mainly cross-sectional and mostly concluded that pain is associated with reduced QOL. The factors framed as predictors of QOL, or independent variables, include presence of pain, pain intensity, and pain severity. However, it is also possible to conceive QOL as a potential contributory psychosocial factor in relation to other pain-related outcomes. Indeed, common QOL measures often incorporate items assessing psychological functioning, such as depression and anxiety, as well as usual daily activities (EQ-5D-5L) [57].

Eight studies provided sufficient data to calculate effect sizes, reflecting mostly large associations between QOL and pain. Six studies found large effects in comparisons between groups with severe vs mild PDN [11,39,45,46]. One study found a medium and negative effect between pain severity and QOL [38]. And another study found a small effect between pain severity and QOL [43]. Twelve additional studies reported negative associations between QOL and pain but did not provide enough information to calculate effect sizes [4,6,14,37,39,42,44,45,48–51].

Table 5. Methodological quality of observational studies [30]

Study	Component Score: A	Component Score: B	Component Score: C	Component Score: D	Overall Score
AL-Mahmood et al. (2018) [51]	5	2	3	2	92.3% (12/13)
Benbow et al. (1998) [37]	4	1	0	1	46.2% (6/13)
Bouhassira et al. (2013) [45]	5	2	3	2	92.3% (12/13)
Currie et al. (2006) [40]	6	0	3	2	84.7% (11/13)
Dobrota et al. (2014) [3]	5	2	3	2	92.3% (12/13)
Galer et al. (2000) [4]	5	2	2	1	71.4% (10/14)
Geelen et al. (2016; 2017) [9, 11]	4	1	3	0	66.7% (8/12)
Gore et al. (2005; 2006) [12, 41]	6	0	2	0	57.1% (8/14)
Hoffman et al. (2009) [43]	6	0	3	2	84.7% (11/13)
Jacovides et al. (2014) [47]	5	0	2	0	50% (7/14)
Kulkantrakorn et al. (2013) [6]	4	0	0	1	38.5% (5/13)
Levterova et al. (2018) [38]	5	2	3	2	92.3% (12/13)
Lewko et al. (2007) [53]	3	0	1	1	38.5% (5/13)
Mai et al. (2015) [14]	4	0	2	2	57.1% (8/14)
Sadosky et al. (2013) [26]	5	0	3	0	61.5% (8/13)
Selvarajah et al. (2014) [48]	5	1	3	1	77% (10/13)
Themistocleous et al. (2016) [49]	5	0	3	0	61.5% (8/13)
Tölle et al. (2006) [42]	5	0	1	0	46.2% (6/13)
Van Acker et al. (2009) [44]	5	2	3	2	92.3% (12/13)
Vileikyte et al. (2009) [54]	5	1	3	2	78.6% (11/14)
Vileikyte et al. (2005) [10]	5	1	3	2	84.7% (11/13)
Wickramasinghe et al. (2016) [50]	5	1	3	1	77% (10/13)
Zelman et al. (2005) [39]	6	0	2	0	57.1% (8/14)
Zelman et al. (2006) [52]	6	0	2	0	57.1% (8/14)

Component Score A: Reporting, score range 0–7; Component Score B: External Validity, score range 0–2; Component Score C: Internal Validity–Bias, score range 0–3; Component Score D: Internal Validity–Confounding (selection bias), score range 0–2.

Table 6. Methodological quality of the RCTs (Cochrane risk of bias assessment tool)

	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding (Performance and Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Otis et al. (2013) [26]	+	?	+	+	+	?
Pfmmater (2012) [55]	?	−	?	−	−	−
Teixeira (2010) [25]	+	?	?	?	−	−

\+ Low risk of bias.

? Unclear risk of bias. High risk of bias.

− RCT = randomized controlled trial.

Quality Assessment

The inter-rater reliability (IRR) in assessing the quality of the 27 included studies was good, at 87.5% agreement between the two raters. There were some minor disagreements, mainly regarding the internal validity of the studies, but these were solved without consulting another member of the research team.

Overall, the methodological quality score, using the Downs and Black quality assessment tool [30], was high in 14 studies [3,4,9,10,12,38,40,43–45,48,50,51,54], medium in four studies [14,39,46,49], and low in five studies [6,37,42,47,53].

The three RCTs were assessed with the Cochrane risk of bias tool, which showed that one study had low risk of bias

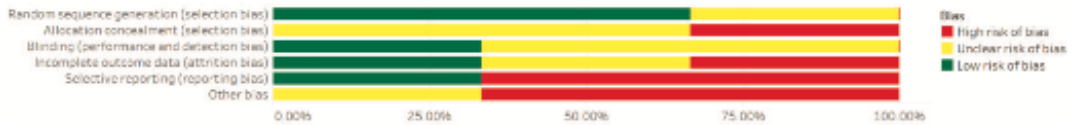

Figure 2. Quality of randomized controlled trials: Cochrane's risk of bias assessment tool.

[26], one study had unclear risk of bias [25], and one study had high risk of bias [55]. The studies were more likely to have low risk of bias for random sequence generation and high risk of bias for potential for selective reporting and "other" bias. More details on the quality assessment of the studies can be found in Tables 5 and 6 and Figure 2.

Discussion

This systematic review was specifically focused on evidence for the role of psychosocial factors and related treatments in relation to outcomes in PDN. The relevant literature was heterogeneous and included few randomized controlled trial designs. The search revealed 27 studies (29 papers). These provide limited evidence of mixed quality for benefits from psychological interventions and some high-quality evidence for associations between depression, anxiety, sleep, and QOL, typically in relation to pain in PDN. There was less evidence for other outcomes, such as physical, social, or emotional functioning. The results of this review identify a need for the further investigation of psychosocial processes in PDN, in relation to a wider set of clinical outcomes guided by a clear theoretical model and for theory-driven treatment development evaluated in larger RCTs.

The identification of only three small RCTs in the review limits the conclusions that can be drawn about the potential efficacy of psychosocial treatment for PDN. These were very small in size, included three distinctly different types of treatment, and produced inconsistent results. The limited number of RCTs of psychological treatments for PDN contrasts with the larger number of reasonably higher-quality RCTs for chronic pain in general, estimated at 35 RCTs [22], and in conditions such as fibromyalgia, for which there are currently around 29 RCTs of CBT [24]. Notably, the lack of trials identified in the current review is consistent with a review of RCTs of psychological treatments for neuropathic pain (not restricted to PDN) [29]. Unfortunately, the current evidence from these studies is not sufficient to support specific recommendations regarding effective psychological treatment for PDN.

The current results provide limited clues regarding the types of psychosocial factors that might influence outcome in PDN and almost exclusively include psychological factors and not social ones. With the exception of fear of negative evaluation, a clear social factor [9], and a study of changing social perception [54], none of the commonly studied social factors (e.g., social support, spousal responses) often found to relate to chronic pain were featured in the available evidence here.

This review found evidence of a mostly consistent positive association between depression and the presence, intensity, or severity of pain in people with PDN, with effects ranging from small to large. This is consistent with a large body of findings in the wider chronic pain literature that consistently links depression and chronic pain outcomes related to depressive symptoms with diabetes [58–62]. Within the current review, the majority of the studies were cross-sectional, which precludes statements about the direction of association between these variables. Drawing on the wider literature, it is likely that there is a bi-directional association between pain and depression. Current results are also consistent with results from a meta-analysis of 27 studies investigating depression in diabetic patients that also showed a significant correlation between depression and complications of diabetes [63].

Another key finding arising from this review was the positive association ranging from medium to large effects between anxiety and pain severity or intensity. Only one of five studies found an inconsistent effect. This overall result is consistent with the broader chronic pain literature, where anxiety is found to either contribute to, or reflect effects of, poor functioning and health [64]. Anxiety and depression are often highly correlated when measured simultaneously in the same sample, and the degree to which the present findings for these variables reflect significantly distinct processes and targets for change is unclear [65,66].

Some of the most frequently studied variables in the context of chronic general or musculoskeletal pain include catastrophizing and acceptance [66,67]. Here, in contrast, only three studies included catastrophizing, and two studies examined some form of acceptance. Overall, these studies did not provide a clear basis for inferring the size of the association or the potential utility of either of these variables for guiding treatment development for PDN. Only one study (two papers) investigated the relationship between pain-related fears and pain. This study showed a large positive association between various fears, including fears of pain, hyperglycemia, falling, and fatigue with increased neuropathic disability, reduced QOL, and pain intensity. This was, as far as we are aware, the first study aiming to specify pain-related fears in a PDN population. That there is only one study of fear in relation to PDN may appear surprising, as the Fear-Avoidance Model is otherwise a widely applied and

productive model of disability in chronic pain in general [68–70]. All of these anxiety-related variables overlap to a degree conceptually and in their measurement. This again can point to the need for conceptual clarity in the choice of variables we investigate.

Evidence of medium to large associations was also found between pain and sleep disruption in the present systematic review, based on three studies. This may be a potentially useful relation, as poor sleep appears common in individuals with neuropathic pain in general and with PDN in particular [52,71]. Poor sleep in the context of chronic pain appears potentially modifiable [72,73] and is a target that could guide treatment development.

The majority of the studies reviewed included QOL. Predominantly, these studies focused on the impact of disease, designed to document the impact of PDN on QOL. Most studies found large associations between pain and poor QOL. This is not surprising, and in fact both direct adverse impacts of PDN on QOL and indirect impacts from depression and anxiety in the context of PDN are well documented [74–77]. The reason that, in a sense, we have turned QOL around and conceived it as a potential influence on other outcomes in PDN, is that we feel that components of QOL, particularly the more behavioral components, such as social and physical activities, are essentially directly modifiable. We know from general chronic pain studies that it is possible to take a direct approach to improving daily activities, for example, and achieve both improvements in these activities and in such outcomes as pain, depression, and other symptoms at the same time [78].

It is notable that there were three additional studies of biofeedback identified during the literature search [79–81]. However, the reported treatment outcomes were physiological, for example, temperature reduction, rather than reports of pain intensity, pain-related functioning, or psychological distress, so these studies were excluded from this systematic review. Thus, future studies exploring biofeedback in this context might benefit from including measures of pain and functioning as outcomes.

Overall, setting aside QOL as a direct treatment target, the available evidence reveals that few modifiable psychosocial factors have been studied in the literature of PDN. Also, when they are studied, they are generally examined in relation to pain as an outcome and not in relation to a wider range of outcomes, such as physical, social, or emotional functioning. In this systematic review, variables like anxiety, depression, and QOL are treated as both outcomes and correlates of outcome. Few studies have examined correlations with these variables, except for pain, pain severity, pain interference, and acceptance of pain. Most of the studies include anxiety and depression as potential independent variables. Only six studies, all cross-sectional, have examined such otherwise frequently studied variables as catastrophizing, fear, or acceptance. What seems to be entirely missing are studies of conventional variables such as beliefs or coping [29] or other facets of psychological flexibility [66]. Hence, the results, as they stand, do not identify specific psychosocial factors or treatment methods that ought to be targeted or applied in PDN, nor do they appear to provide clear guidance for treatment development, other than to highlight the potential role of emotional functioning, sleep, and perhaps a direct approach to daily functioning. The very limited number of studies of psychological treatments or psychosocial factors in PDN compared with other chronic pain conditions, particularly in the context of the clear treatment needs in PDN, raises questions as to why this is the case and what might be the barriers to psychological studies in this population.

Several limitations of this systematic review need to be considered. Our defined population was explicitly adults; therefore, the results of this review cannot be generalized to children and adolescents. We used broad search terms for PDN, psychosocial factors, and psychological interventions to identify all the eligible studies; however, given the broad nature of the search, it is possible that we may have missed studies. We calculated effect sizes based on the given means and SDs, but not all studies provided sufficient data for effect sizes. We collapsed multiple between-group analyses into dichotomous comparisons to enable comparison across studies to minimize paired comparisons; however, this may have eliminated a more subtle understanding of the association between psychosocial factors an pain outcomes.

Future research is encouraged to examine a wider array of theoretically based psychosocial factors than currently done and to more deeply pursue the utility of such current theoretical models as the Fear-Avoidance Model and the Psychological Flexibility Model. Naturally, studies from either of these models can incorporate the role of emotional functioning, and ought to do so, as this domain is the one that is most clearly highlighted here as relevant, and it appears that the Psychological Flexibility Model can address sleep [72,82].

There appears to be a clear potential for nonpharmacological, particularly psychological, treatments for PDN. The current review does not, however, clarify specific psychological processes to target, and certainly not comprehensively. The absence of fully powered, high-quality studies of psychological treatment for PDN found here is notable. Future trials may explore questions around nonparticipation and dropout and ways to enhance access and acceptability in addition to the core questions of effectiveness. It is recommended that future treatments aim not only to treat pain but also to improve other aspects of the condition, such as emotional and physical functioning, and participation in life in general. The challenge here then seems to be the identification of a model of treatment processes with the potential to produce these general results.

Authors' Contributions

KK, the first author, responsible for the work as a whole, contributed to the design of the project, searched the selected databases, screened the titles, selected the eligible articles, did the data extraction and methodological quality check, interpreted the results, and produced the first draft of the manuscript. LM contributed to the conception and research plan, to the final selection of the articles, critically revised the manuscript, and approved the final version. KW contributed to the design of the study, contributed to the final selection of the articles, critically evaluated the manuscript, and approved the final version. WS acted as the second reviewer of the research and contributed to the data extraction and methodological quality check. SK acted as a third reviewer and contributed to the search of the databases, screening of the titles and abstracts, selection of the eligible articles, data extraction, and quality assessment. All authors contributed to critically revising the manuscript and approved the final submitted version. None of the authors declares a conflict of interest or any financial or other relationship that might lead to any conflict.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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Might psychological flexibility processes and Acceptance and Commitment Therapy (ACT) apply in adults with painful diabetic neuropathy? A cross-sectional survey

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ABSTRACT

Painful diabetic neuropathy (PDN) is a distressing and disabling condition. There is, surprisingly, relatively little research into the role of psychological variables related to PDN. The aim of this study was to investigate the association between psychological flexibility, daily functioning, and distress in people with PDN. This cross-sectional study included 225 participants who were recruited from hospital services and online. In correlation analyses, acceptance of pain was shown to be negatively correlated with pain intensity ($r = -0.21$, $p < 0.01$), pain distress ($r = -0.25$, $p < 0.01$), functional impairment ($r = -0.38$, $p < 0.01$), depression severity ($r = -0.41$, $p < 0.01$), and depression impact ($r = -0.41$, $p < 0.01$). Cognitive fusion correlated positively with pain intensity ($r = 0.14$, $p < 0.05$), functional impairment ($r = 0.24$, $p < 0.01$), depression severity ($r = 0.44$, $p < 0.01$), and depression impact ($r = 0.20$, $p < 0.01$). Committed action also correlated negatively with functional impairment ($r = -0.22$, $p < 0.01$), depression severity ($r = -0.43$, $p < 0.01$), and depression impact ($r = -0.21$, $p < 0.01$). In regression analyses, the four variables representing psychological flexibility accounted for significant variance in all the equations except in the case of pain distress. However, in some cases the variance accounted for was less than that accounted for by pain intensity. For example, in the equation for functional impairment, pain intensity accounted for 32.2% of variance, while psychological flexibility accounted for 6.8% of variance. These results suggest that psychological flexibility may play a smaller role, relative to pain intensity, in the context of PDN as compared to the larger populations of chronic, mostly musculoskeletal, pain. The reliability and generalisability of these results need to be established.

1. Introduction

The World Health Organization (WHO, 2016) estimates that approximately 422 million adults live with diabetes mellitus (DM) worldwide. If DM is poorly managed, it can lead to complications, such as kidney failure, heart disease, stroke, blindness and neuropathy. The most common type of neuropathy caused by DM is painful diabetic neuropathy (PDN), affecting 25–30% of people with DM (Daousi et al., 2004; Davies, Brophy, Williams, & Taylor, 2006; Geelen et al., 2017). PDN is a complex condition affecting the peripheral nervous system (Treede et al., 2007), resulting in loss of sensation, numbness, and a burning, sharp, electrical, stinging pain in the affected area, which often worsens at night (Bouhassira et al., 2005; Daousi et al., 2004; Davies et al., 2006; Geelen et al., 2017). It is known to negatively affect physical and mental health, to reduce overall quality of life (Benbow, 1998; Fernando et al., 2013; Galer, Gianas, & Jensen, 2000; Gore et al., 2005; Van Acker et al., 2009; Vileikyte et al., 2009), and to impact on work, social life, general activities, and sleep (Geelen et al., 2017). There are few studies of the role of psychological processes in people with PDN (Kioskli, Scott, Kylakos, Winkley, & McCracken, 2019) and these have focused on a narrow set of variables, such as depression and anxiety (Gore et al., 2005), and fears (Geelen et al., 2017).

Forms of cognitive behavioural therapy (CBT) are the most often used psychological treatments for chronic pain. These include contextual forms of CBT, such as Acceptance and Commitment Therapy (ACT) (Hayes, Strosahl, & Wilson, 1999; McCracken & Morley, 2014; McCracken & Vowles, 2014). ACT is a form of CBT that includes methods of acceptance, mindfulness and behaviour change (Hayes, Strosahl, & Wilson, 2003) and explicitly focuses on increasing psychological flexibility (PF; Hayes, Villatte, Levin, & Hildebrandt, 2011). PF

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is a model of wellbeing and performance that includes six related processes: acceptance, cognitive defusion, present moment awareness, self-as-context, values, and committed action (Hayes, Luoma, Bond, Masuda, & Lillis, 2006). This is sometimes referred to as a focus on openness to experiences, awareness of the present moment, and engagement in actions that are guided by values and goals (Hayes et al., 2011). The current literature indicates that ACT and closely allied approaches are at least as effective as other psychological approaches for managing chronic pain (Hann & McCracken, 2014).

Current treatment options for PDN are mainly pharmacological. There are only four studies of psychological treatments for PDN, including CBT, mindfulness, mindfulness-based stress reduction (MBSR) and thermal biofeedback assisted relaxation (Nathan et al., 2017; Otis et al., 2013; Pfammatter, 2010; Teixeira, 2010). The results from the mindfulness study (Teixeira, 2010) suggested a small between-group effect in the mindfulness group on quality of life ($d = -0.16$, 95% CI: −1.1 - 0.78) and large effect on sleep ($r = 0.53$, 95% CI: 0.048–0.813). Evidence from the biofeedback study (Pfammatter, 2010) did not produce any statistically significant results. The CBT study (Otis et al., 2013), an RCT (N = 20), showed significant decreases in pain, pain interference and depression levels in the CBT group, at post-treatment and follow-up ($d = 0.68–0.91$), compared to the control group. Results from the MBSR study (Nathan et al., 2017) showed that more than half of participants in the experimental group (19/30) improved in depression, pain interference, quality of life, catastrophizing and function. Overall, their results are promising and, at the same time, due to small sample sizes or small effects, show no clear evidence-based psychological approach for PDN.

Previous studies of chronic pain provide support for the role of PF in relation to well-being and daily-functioning, in people with mixed chronic musculoskeletal pain conditions (McCracken, Gauntlett-Gilbert, & Vowles, 2007; McCracken & Velleman, 2010; Vowles, McCracken, & Eccleston, 2008), chronic low back pain (Mason, Mathias, & Skevington, 2008), and fibromyalgia (Yu, Norton, Almarzooqi, & McCracken, 2017). Preliminary evidence of this type has led in turn to successful treatment trials of ACT in these conditions (Hann & McCracken, 2014). We simply do not know whether the results from studies of PF in the context of chronic musculoskeletal pain will be replicated in the context of PDN, again, a condition for which there are very few psychological studies, and none focused on PF.

The complex and particularly intractable qualities of PDN are important as motivators for research into the role of PF. The prospects for pain control are practically very limited, even when compared to other pain conditions, and so an approach that supports the capacity to function without pain control, and in the midst of multiple co-morbid symptoms, appears relevant to this condition. However, no published studies have yet explored either the suitability of ACT or the applicability of PF to individuals with PDN.

Finally, there is one more motivation for the study of PDN in a context of many studies of other pain conditions. It appears that neuropathic pain conditions in clinical practice are implicitly regarded as mainly a physical problem with relatively little psychological input (Kioskli, Scott, Winkley, Kylakos, & McCracken, 2019), possibly because that pathology underlying the pain appears undeniable. This conclusion is supported by evidence from large cohorts of people seeking specialty treatment for chronic pain where few if any report diagnosis of neuropathic pain (Mason et al., 2008; McCracken & Velleman, 2010; Yu et al., 2017). We argue that, in order to overcome this bias against access to psychosocial thinking and treatment development for PDN, evidence for the role of psychological factors must be shown in this condition specifically.

The purpose of the present study is to survey people with PDN and examine the role of PF in relation to their daily functioning, including emotional functioning. Our research question is whether PF, here including acceptance, cognitive defusion, committed action, and self-as-context, is relevant and potentially beneficial for people with PDN. We predicted that each process measured here would be relevant and that a potentially important role would be shown in significant correlations between measures of PF and measures of pain and daily functioning in this group, and significant increments of explained variance in multivariate analyses.

2. Methods

2.1. Study design and participants

The current study was a cross-sectional survey of adults with Type 1 and Type 2 diabetes and PDN. Participants were included regardless of any treatment they were receiving. The sample was recruited from pain and diabetes hospital services, from Diabetes UK (DUK), other websites designed to support people with pain, and via social media (i.e. Twitter). The recruitment started on 6 of February 2018 and finished on 6 of May 2018.

2.2. Sample size

A priori estimation was used to determine the required sample size based on several considerations. First, for multiple regression analyses, we based our estimate on similar studies (Billingham, Whitehead, & Julious, 2013; Chilcot et al., 2015). We also based it on modelling a regression equation with 12 predictors and an effect size (Muller & Cohen, 1989) of $f^2 = 0.15$ (medium effect), with power set at 0.80. This suggested a need for a sample size of at least 127. Finally, we also considered possible missing data, and the need for an adequate sample size for secondary validity analyses of the instruments being used, as well as sensitivity analyses based on the mode of recruitment. We thus aimed to recruit a minimum of 200 participants.

2.3. Procedure

Ethical approval was gained for this study (Surrey Research Ethics Committee, 29/1/2018. Ref: 17/LO/2047). Informed consent was obtained from all participants, described below in more detail.

The inclusion criteria for this study were aged 18 years or more, living in the UK, having either a confirmed or self-reported diagnosis of diabetes mellitus (DM), having suffered from PDN for the last three months or more, having the ability to take part in the study, and the ability to provide informed consent. Diabetes and neuropathy diagnosis were assessed, using two participant self-report questions and the validated screening questionnaire, Douleur Neuropathique 4 (DN4). DN4 was not administered to the whole sample, but to a subgroup of participants, as it was not initially a high priority concern to obtain this kind of screening data, and in order to reduce the length of the survey. Participants recruited from the hospital services also had a physician's diagnosis.

Potential participants who were not able to understand verbal explanation or written information in English were excluded from the study, as no resources were available to translate the survey or to produce and validate the standardized measures being used in other languages.

Participants were recruited either online or face-to-face through hospital services. In particular, within the hospital services, participants were identified by diabetes and pain clinical care teams. A member from our research team then approached the potential participants, in the relevant outpatient clinics, explained the study and answered questions. Participants who agreed to take part then gave consent and received the recruitment pack.

A total of 120 participants were initially approached in person. Of the 120 invited this way, 60 did not meet the inclusion criteria (N = 25 not being diagnosed with diabetes, N = 35 suffering from neuropathy due to other causes than diabetes), and 38 declined to take part. Reasons for non-participation included, the length of the questionnaires

(N = 16), not being able to understand written information in English (N = 10), and some eligible participants declined to give a reason (N = 12). A total of 14 completed the pen-and-paper version of the presented survey. Two out of the 14 participants did not adequately complete the questionnaire and were excluded. In total 12 participants were recruited from hospital services.

Online recruitment was conducted through sending targeted online invitations to diabetes organisations with an online presence and through social media. An email was sent to the charity Diabetes UK (DUK), explaining the study and the inclusion criteria of participants and asking to publicise it through any available means, such as special interest forums and their website. Within the email, there was also a link to the online version of the survey. DUK posted the link on the recruitment page (https://www.diabetes.org.uk/research/take-part-in-research) and forum. Recruitment was also done via Twitter and two discussion forums sponsored by charity supported websites, 'Pain Support' (http://painconcern.org.uk/how-we-help/forum/) and 'Pain Concern'(https://painsupport.co.uk/). Particularly, 130 people were recruited from DUK's website, 40 from DUK's forums, 7 from Twitter, 17 from Pain Support forum and 19 from Pain Concern forum. In total 213 participants were recruited from online sites. This dual method of recruitment, in clinic and online, was aimed at including a wider sample of people suffering from PDN and achieving the targeted sample size.

2.4. Measures

The participants who agreed to take part in the survey completed a series of psychometrically validated assessment measures. The following additional variables were assessed through self-report questions: age, gender, ethnicity, education, work status, marital status, type of diabetes, presence of neuropathy, duration of pain, and specific pain locations. The survey was administered via paper or a widely available survey platform, Bristol Online Survey (BOS, https://www.onlinesurveys.ac.uk/). This is an easy to use portal to create a survey and used by many institutions. BOS is flexible and does not require any technical knowledge to set-up the survey or collect the data.

2.4.1. Chronic pain acceptance questionnaire (CPAQ-8)

The CPAQ-8 is a measure of acceptance of chronic pain. It includes engagement in activities while experiencing pain and willingness to experience pain without trying to control or avoid it (McCracken & Velleman, 2010; McCracken, Vowles, & Eccleston, 2004). CPAQ-8 is based on the 20-item questionnaire, and this version consists of 8 items and has also been fully validated (Fish, McGuire, Hogan, Morrison, & Stewart, 2010). Items are rated on a scale from 0 (never true) to 6 (always true). Higher scores reflect greater acceptance of pain. In the current sample, the CPAQ-8 demonstrated good internal consistency (Cronbach's $\alpha = 0.87$).

2.4.2. Cognitive fusion questionnaire (CFQ-7)

The CFQ-7 is a measure of cognitive fusion (Gillanders et al., 2014). Cognitive fusion refers to a domination of cognitive influence over direct experiential influence on behaviour, and a lack of separation between the content of the thoughts and the situations or people to which they refer. Cognitive defusion, on the other hand, is the ability to see thoughts as just thoughts, and not as essential reflections of events as they are directly experienced. The CFQ-7 consists of seven items rated on a 1 (never true) to 7 (always true) point scale. An early version of the CFQ has been validated in chronic pain samples based on significant predicted correlations with acceptance and daily functioning in people with chronic pain (McCracken, DaSilva, Skillicorn, & Doherty, 2014). The updated version was used in the present survey. In the current sample, the CFQ-7 demonstrated good internal consistency (Cronbach's $\alpha = 0.95$).

2.4.3. Committed action questionnaire (CAQ-8)

The CAQ-8, is an eight-item measure of committed action, a facet of PF (McCracken, 2013; McCracken, Chilcot, & Norton, 2014). Committed action is the ability to persist with actions that are guided by goals, including when this runs into discouraging experiences and to change these actions when they are shown to be ineffective. Responses to the items were rated from 0 (never true) to 6 (always true). Out of the eight items four are positively keyed and four negatively keyed. Scores from the CAQ-8 have demonstrated relations with measures of acceptance, and of emotional, physical, and social functioning in people with chronic pain, supporting construct validity (McCracken, Chilcot, et al., 2014). In the current sample, the CAQ-8 demonstrated good internal consistency (Cronbach's $\alpha = 0.81$).

2.4.4. Douleur neuropathique 4 (DN4)

Presence of neuropathic pain was assessed with a screening measure called DN4. It consists of four interview questions and has also been psychometrically validated as a self-report measure (Bouhassira et al., 2005). It has a specificity of 83% and sensitivity of 90% (Spallone et al., 2012). In the current sample, the DN4 demonstrated adequate internal consistency (Cronbach's $\alpha = 0.75$). This questionnaire was only administered to a subsample (N = 75), to reduce the length and burden of the survey. The subsample was selected from their response to a question at the end of the survey asking if they would be willing to take part in further research, if they answered 'yes', we contacted them and asked them to respond to the DN4. The purpose was to validate the self-report method for determining the diagnosis of PDN used in the full sample.

2.4.5. Pain scale

Pain intensity and pain-related distress were assessed through four validated questions using 0 (no pain/distress) to 10 (worst possible pain/distress) numerical ratings. Participants were asked to rate their pain right now and in the past week, and how distressing their pain is right now and in the past week (Jensen, Turner, Romano, & Fisher, 1999; Von Korff, Ormel, Keefe, & Dworkin, 1992). In the current sample the reliability, of pain intensity and pain distress scale, was calculated with the Spearman-Brown formula, due to the fact that each scale has only two items and is was $r = 0.86$ in each case (Eisinga, Grotenhuis, & Pelzer, 2012).

2.4.6. Patient health questionnaire (PHQ-9)

The PHQ-9 is a widely used, reliable and validated, measure used as an index for depression severity. It includes ten items based on DSM-IV. The first nine items reflect severity of depression symptoms and each is rated on a scale from 0 (not at all) to 4 (nearly every day). The last item, item ten, is a measure of impact of depression and is rated from 'not difficult at all' to 'extremely difficult' - this item was used as an additional variable to study here because within the psychological flexibility model the impact of symptoms of functioning is regarded as a particularly important potential outcome in treatment. The higher score for the sum of the nine items indicates higher levels of depression severity (Kroenke, Spitzer, & Williams, 2001). In the current sample, the PHQ-9 demonstrated good internal consistency (Cronbach's $\alpha = 0.84$).

2.4.7. Self experiences questionnaire (SEQ)

The SEQ is a 15-item self-report measure of self-as-context, within the PF model (Yu, McCracken, & Norton, 2016). This "contextual self" is defined as a sense of self that is not based upon self-evaluations and is separate from one's thoughts and feelings. This could also be referred as, taking a point of view on one's psychological experiences, seeing oneself as distinct from one's psychological experiences, or as "perspective taking". All items are rated on a scale from 0 (never true) to 6 (always true). All items are positively keyed, and higher scores indicate higher PF. The construct validity of the SEQ has been supported in demonstrated significant expected correlations with acceptance,

committed action, and decentering, and with depression and daily functioning in people with chronic pain (Yu et al., 2016). In the current sample, the SEQ demonstrated good internal consistency (Cronbach's α = 0.98).

2.4.8. Work and social adjustment scale (WSAS)

The WSAS is a five-item, reliable and validated self-report measure of impairment in work and social functioning, or as we label here, "functional impairment" (Mundt, Marks, Shear, & Greist, 2002). WSAS items refer to work, home management, social and private leisure, and relationships. Each item is rated from 0 (no impairment) to 8 (very severe impairment). The validity of the WSAS is supported by significant correlations with measures of psychiatric symptoms and it is shown to be sensitive to the effects of treatment (Mundt et al., 2002). In the current sample, the WSAS demonstrated good internal consistency (Cronbach's α = 0.93).

2.5. Statistical analyses

The collected data were analysed with the Statistical Package for Social Science (version 18.0 IBM, SPSS). Limited missing data in the standardized inventories were substituted by mean imputation. The total sample size was 225 participants. Descriptive statistics, including means and standard deviations (SDs) for continuous variables and frequencies and percentages for categorical variables, were calculated for the sample.

All standardized measures were scored according to their standard instructions. The variables consisting the PF facets were: acceptance of chronic pain (CPAQ-8), cognitive fusion (CFQ-7), committed action (CAQ-8), and self-as-context (SEQ). The dependent variables of the study were pain and pain-related distress (pain scale), functional impairment (WSAS), depression (PHQ-9), and depression impact (PHQ-9 item 10). Preliminary analyses included *t*-tests and correlation analyses examining relations between the pain outcomes and functioning variables and the PF variables with individual's background characteristics.

Three sets of analyses were conducted to address the main purpose of this study. The first set included correlation analyses between the four PF variables, with pain, functional impairment, and depression variables. These analyses were conducted to first identify significant unadjusted relationships between these variables in order to then proceed to a multivariate approach with linear, hierarchical, multiple regressions. Multiple regression analyses were designed both to consider and statistically control the role of age, education, sex, pain duration, and pain intensity, and to examine the proportion of variance accounted by acceptance of chronic pain, cognitive fusion, committed action, and self-as-context, uniquely and combined, in relation to the measures of participant's functioning.

3. Results

3.1. Sample characteristics

A total of 225 people participated in this survey. Mean age of all participants was 52.05 (SD = 12.06) years. Women represented 64.9% of the sample and white ethnicity 82.2%. Mean years of education was 14.98 (SD = 3.76) and mean years pain duration was 7.16 (SD = 9.02). Employment status was categorized as follows: full-time employment (24%), employed part-time due to pain (22%), employed part-time due to other reasons (13%), retired (24%), unemployed due to pain (10%), and full-time student (7%). Mean DN4 score was 7.15 (SD = 2.39) and 92.7% exceeded the cut-off, an overall score of 4, for neuropathic pain. The 12 participants recruited from hospital services and 213 from online did not differ on background variables or the measures of psychological flexibility or pain outcome measures and were treated as one sample.

Table 1
Means and standard deviations for standardized psychological flexibility variables, health and functionality outcome variables ($N = 225$).

	Possible Range	Sample Mean	Standard Deviation
Pain intensity (Rating Scales)	0–10	4.31	2.24
Pain distress (Rating Scales)	0–10	4.52	2.43
Functional impairment (WSAS)	0–40	17.67	11.48
Depression severity (PHQ-9 items 1–9)	0–27	12.05	7.00
Depression impact (PHQ-9 item 10)	0–3	1.83	0.64
Acceptance of pain (CPAQ-8)	0–48	25.01	4.88
Cognitive fusion (CFQ)	7–49	24.33	11.06
Committed action (CAQ-8)	0–48	21.08	8.16
Self-as-context (SEQ)	0–90	40.98	21.17

3.2. Preliminary analysis

Each primary variable was examined for normality by using histograms, Q-Q plots, and indices of skewness and kurtosis. None of the primary measures in this study produced significantly skewed distributions or outliers expected to adversely affect correlation-based analyses. The total scores of all measures were considered normally distributed. See Table 1 for means, ranges and standard deviations for the primary study variables.

Pain intensity and distress variables differed significantly by gender, with men reporting higher scores of pain intensity, $t = -3.09$, $p < 0.01$, and pain-related distress, $t = -2.86$, $p < 0.01$. Participants of white ethnicity reported lower scores in terms of committed action, $t = -2.64$, $p < 0.01$, functional impairment, $t = -2.96$, $p < 0.01$, and self-as-context, $t = -3.82$, $p < 0.01$, than the non-white group of participants. Employed participants scored significantly lower in terms of committed action, $t = -2.73$, $p < 0.01$, functional impairment, $t = -2.97$, $p < 0.01$, and self-as-context, $t = -3.44$, $p < 0.01$ variables than those who are not employed.

Preliminary correlation analysis showed that age was correlated with committed action, depression severity, and self-as-context, $r = -0.23$, $p < 0.01$; $r = 0.19$, $p < 0.01$, and $r = -0.24$, $p < 0.01$ respectively. Years of education was found to be correlated with all primary variables except cognitive fusion, including pain intensity: $r = 0.20$, $p < 0.01$; acceptance of pain: $r = -0.16$, $p < 0.05$; committed action: $r = -0.20$, $p < 0.01$; depression severity: $r = 0.21$, $p < 0.05$; functional impairment: $r = 0.21$, $p < 0.01$; self-as-context: $r = -0.14$, $p < 0.05$. Duration of pain was not significantly correlated with any of the variables.

3.3. Correlation analyses

The four primary PF variables were not found to be correlated with each another at a level that would suggest problems of multicollinearity in regression analyses ($r < 0.80$, Grewal, Cote, & Baumgartner, 2004). In fact, the highest correlation between these variables was $r = 0.54$. Please see Table 2.

Table 2
Primary correlation analysis among psychological flexibility variables ($N = 225$).

	1	2	3	4
1. Acceptance of pain	–			
2. Cognitive fusion	-.25*			
3. Committed action	.40**	-.42**		
4. Self-as-context	.27**	-.20**	.54**	–

*p < 0.05, two-tailed, **p < 0.01 two-tailed.

Table 3
Correlations between psychological flexibility variables, health and functioning, and pain.

	Pain intensity	Pain distress	Functional impairment	Depression severity	Depression impact
Pain intensity	–	.87**	.57**	.51**	.40**
Acceptance of pain	-.21**	-.25**	-.38**	-.41**	-.41**
Cognitive fusion	.14*	.12	.24**	.44**	.20**
Committed action	-.05	-.12	-.22**	-.43**	-.21**
Self-as-context	-.05	-.07	-.07	-.31**	.00

*p < 0.05, two-tailed. **p < 0.01 two-tailed.

Correlations between acceptance of pain, cognitive fusion, self-as-context, and committed action and pain intensity with pain-related distress, functional impairment, depression severity, and depression impact are included in Table 3. Pain intensity positively correlated with pain distress, $r = 0.87$, $p < 0.01$, functional impairment, $r = 0.57$, $p < 0.01$, depression severity, $r = 0.51$, $p < 0.01$, and depression impact, $r = 0.40$, $p < 0.01$. Acceptance of pain negatively correlated with pain intensity $r = -0.21$, $p < 0.01$, pain distress, $r = -0.25$, $p < 0.01$, functional impairment, $r = -0.38$, $p < 0.01$, depression severity, $r = -0.41$, $p < 0.01$, and depression impact, $r = -0.41$, $p < 0.01$. Cognitive fusion positively correlated with pain intensity $r = 0.14$, $p < 0.05$, functional impairment, $r = 0.24$, $p < 0.01$, depression severity, $r = 0.44$, $p < 0.01$, and depression impact, $r = 0.20$, $p < 0.01$. Additionally, committed action negatively correlated with and functional impairment, $r = -0.22$, $p < 0.01$, depression severity, $r = -0.43$, $p < 0.01$, and depression impact, $r = -0.21$, $p < 0.01$. Lastly, self-as-context negatively correlated only with depression severity, $r = -0.31$, $p < 0.01$.

3.4. Multiple regression analyses

Multiple regression analyses were conducted to examine the unique and combined role of PF variables, after adjusting for individuals' characteristics and pain intensity, in relation to the measures of health and functioning: pain-distress, functional impairment, depression severity, and depression impact. Hence four regression equations were conducted.

The potential predictors were tested hierarchically in each of these equations. Participants' age, gender, education and duration of pain were firstly tested and retained in the equations when significant (first block, $p < 0.05$ to enter, $p > 0.10$ to remove). Afterwards, the pain intensity average score was entered to control its contribution to the prediction of each criterion variable (second block). Finally, acceptance of pain, cognitive fusion, committed action, and self-as-context scores were entered together in a single block to examine their contribution. The regression results are shown in Table 4.

Education was entered and retained as a significant predictor at entry into all the equations. However, the regression coefficient for education did not remain significant in the final step of all the regression equations. It should be noted that education accounted for modest increments of variance at entry, no more than 7.7%. Gender and duration of pain were not significant predictors at entry in the equation for depression impact, depression severity or functional impairment. Gender was a significant predictor of pain distress, with men experiencing more pain distress than women, explaining 3.1% of variance. Gender did not remain significant in the final step of the regression equation. Finally, age was a significant predictor of both depression impact and depression severity and accounted for a 3.0% and a 2.3% increment of variance, respectively. As age increased, depression impact and depression severity also increased. Age remained significant only in the final step of depression impact regression equation.

The pain intensity variable was a significant predictor at entry and remained significant in all the equations. In the equation for functional impairment, pain intensity had the largest regression coefficient and the ΔR^2 value, higher than that of the four PF variables combined, reflected

Table 4
Multiple regression analyses of psychological flexibility variables with measures of health and functioning.

Block	Predictor	Beta (final)	ΔR^2 (block)	sr^2	Adjusted total R^2
Pain distress					
1	Duration of education	.100**	.061**	.009	
2	Gender	-.015	.031*	.000	
3	Pain intensity	.851**	.671**	.642	
4	Acceptance of pain	-.012	.003	.000	
	Cognitive fusion	-.027		.001	
	Committed action	-.072		.003	
	Self-as-context	.034		.001	.757**
Functional impairment					
1	Duration of education	.081	.045**	.006	
2	Pain intensity	.532**	.322**	.264	
3	Acceptance of pain	-.218**	.068**	.037	
	Cognitive fusion	.062		.003	
	Committed action	-.075		.003	
	Self-as-context	.053		.002	.417**
Depression severity					
1	Duration of education	.061	.042**	.003	
2	Age	.079	.030*	.006	
3	Pain intensity	.436**	.233**	.178	
4	Acceptance of pain	-.158**	.187**	.019	
	Cognitive fusion	.228**		.041	
	Committed action	-.165*		.015	
	Self-as-context	-.064		.003	.473**
Depression impact					
1	Duration of education	.173**	.077**	.027	
2	Age	.131*	.023*	.015	
3	Pain intensity	.314**	.132**	.092	
4	Acceptance of pain	-.313**	.126**	.075	
	Cognitive fusion	.000		.000	
	Committed action	-.136		.010	
	Self-as-context	.237**		.039	.334**

*p < 0.05, two-tailed, ** p < 0.01, two-tailed.

32.2% of the variance. In the equation for depression severity, pain intensity once again had the largest regression coefficient and the ΔR^2 value, close to that of the four PF variables combined, reflected 23.3% of the variance. In the equation for pain distress, pain intensity had the largest regression coefficient and the ΔR^2 value, higher than that the four PF variables combined, reflecting 67.1% of the variance. In the equation for depression impact, pain intensity had the largest regression coefficient and the ΔR^2 value, close to that of the four PF variables combined, reflected 13.2% of the variance.

The combination of the four variables representing PF variables accounted for a significant increment of variance in all the equations except in the case of pain distress. In the equation for functional impairment, PF variables accounted for 4.5% of the variance, although only the coefficient for acceptance of pain was significant. In the case of depression severity, acceptance of pain, cognitive fusion and committed action had significant regression coefficients and the variance accounted for was 7.5%. In the case of the pain distress, no significant

regression coefficient was found from among the PF variables. In the case of depression impact, acceptance of pain and self-as-context had significant regression coefficients and the variance accounted for was 11.4%.

Standardized regression coefficients and the squared semi-partial correlation coefficients reveal the relative role of the four separate processes when considered together. Mean proportions of unique variance contributed (sr^2) from all the equations were as follows: acceptance of pain, 0.033, cognitive fusion, 0.011, committed action, 0.008, pain intensity, 0.294, and self-as-context, 0.011.

4. Discussion

PDN is a complex condition and one of the most distressing complications of DM (Galer et al., 2000; Selvarajah et al., 2014). Despite this, existing studies of psychological variables mainly focus on pain intensity as outcome in relation to depression and anxiety without exploring the other potentially therapeutic psychological processes. For the first time in a study of PDN, facets of PF were carefully assessed, using validated questionnaires, and examined in relation to standard measures of pain and functioning.

This study demonstrated significant correlations between PF variables and functional impairment, depression severity, and depression impact in people with PDN. These results are consistent with the results of previous studies that support the role of PF in people with general, usually musculoskeletal, pain, including studies particularly focused on acceptance of pain (Mason et al., 2008; McCracken, 1998; Nicholas & Asghari, 2006; Viane et al., 2003), cognitive defusion (McCracken, DaSilva, Skillicorn, & Doherty, 2014), mindfulness (McCracken, MacKichan, & Eccleston, 2007) and value-based action (McCracken et al., 2007), and committed action (McCracken, 2013).

In this study, we found mostly small correlations between PF and the dependent variables, functional impairment, depression severity, and depression impact, and relatively larger correlations between pain and some of these same variables, particularly so for functional impairment, less for the depression variables. While PF appears as a plausible contributor, pain severity generally appears to play a more important role in relation to daily functioning in PDN. This result is different in this sense from studies of other populations where the role of PF facets in daily functioning and wellbeing appears greater and the role of pain itself appears smaller, including studies of mixed pain conditions (McCracken & Velleman, 2010; McCracken & Zhao-O'Brien, 2010), low back pain (Mason et al., 2008), fibromyalgia (Wicksell et al., 2012; Yu et al., 2017) and headache (Almarzooqi, Chilcot, & McCracken, 2017; Foote, Hamer, Roland, Landy, & Smitherman, 2015). Taking into account that the role of PF is smaller than expected, this could be due to as yet unidentified differences in the experience of neuropathic pain. There are so few psychological studies in neuropathic pain, however, it is too soon to confirm the current results or propose an explanation.

Studies investigating outcomes following treatment have demonstrated a moderate-sized negative relationship between changes in PF variables and pain interference (Wicksell, Ahlqvist, Bring, Melin, & Olsson, 2008) and pain-related anxiety, depressive symptoms, physical and psychosocial disability (McCracken & Gutiérrez-Martínez, 2011; McCracken & Jones, 2012; Vowles, McCracken, & O'Brien, 2011). These results suggest that if PF is increased this would lead to the improvements in a wide range of outcomes. It remains to be seen if this would happen in PDN.

Regression analyses here show that PF variables may play a significant role in functional impairment, depression severity and depression impact, even when other relevant factors are considered, including background variables and pain intensity. Acceptance of pain appeared to contribute the greatest proportion of variance among the PF variables. In general, this suggests that these variables may afford a route toward improved functioning that is independent of pain severity in this population.

It may be worth mentioning that compared to previous pain research our sample was older (by approximately 10 years) (i.e. McCracken & Velleman, 2010), but it was consistent with PDN research (i.e. Geelen et al., 2017). Participants in the current study were more likely to be employed either part-time or full-time, and they reported a lower level of acceptance of pain than other studies. The sample recruited from hospital services and online did not appear to differ. It remains the case, however, that the applicability of the current results to specific subpopulations with PDN will need to be further examined.

As far as we are aware, only four studies of psychological treatments have been conducted including individuals with PDN, most of them were either small in scale or produced limited results (Nathan et al., 2017; Otis et al., 2013; Pfammatter, 2010; Teixeira, 2010). Clearly more research needs to be done, including into the structure and mode of delivery and into the choice of treatment methods. It appears reasonable, based on present findings, to next incorporate the components of PF into a pilot or feasibility trial.

ACT has been applied successfully to individuals with chronic pain and has growing support (Hann & McCracken, 2014; McCracken & Morley, 2014; Veehof, Trompetter, Bohlmeijer, & Schreurs, 2016). We know in particular that online treatment is increasingly used. A brief online treatment for chronic pain in general, based on ACT, has been demonstrated feasible within a mixed specialty pain treatment population in the UK (Scott, Chilcot, Guildford, Daly-Eichenhardt, & McCracken, 2018). This type of delivery format and similar content could provide efficient means for further treatment development for PDN.

This study addresses new questions and produces new findings. At the same time, it has a number of limitations. Because of the cross-sectional design and reliance on self-report measures, it can include biases. Self-reports may include some participants not reporting their actual behaviour and views, which may compromise the accuracy of the results. Also, it did not include either analysis of variables over time or an experimental manipulation. No conclusions about causal relations between PF and functioning are possible. Furthermore, the questionnaire was also accessed online anonymously. This means diagnoses could not be verified. This also makes it possible for participants to access it more than once, although the length of the questionnaire certainly would discourage participants from doing this. Also, recruitment among those seeking treatment in the hospital services was limited (10%). It is possible that results may have been different if that recruitment had been more successful. Lastly, our results cannot be automatically generalized to any specific groups within the larger population of people with PDN, groups characterized by specific ethnicity, age, comorbidities, and other factors. If the sample had been different in any of these ways, the results could have been different.

In conclusion, based on the collected data of this cross-sectional observational study, facets of PF are associated with pain, emotional experiences, and difficulties experienced in daily life activities of individuals with PDN. Meanwhile, the unexpected relatively larger role that pain intensity appears to play in the PDN population calls for replication. If a significant role for pain itself is confirmed as reliable, perhaps we need to search more vigorously for effective remedies for pain itself. Further study of psychological factors in general in the context of PDN is encouraged to support the design and evaluation of psychological treatments for individuals suffering from PDN, a condition that has been the subject of very few psychological treatment studies. A psychological treatment focusing on psychological flexibility, rather than on symptom control, may represent an important new option, an addition to the current almost complete reliance on analgesic medication only.

Conflicts of interest

None to declare.

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Original Research Article

Online Acceptance and Commitment Therapy for People with Painful Diabetic Neuropathy in the United Kingdom: A Single-Arm Feasibility Trial

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Abstract

Objective. This study aimed to assess the feasibility of online Acceptance and Commitment Therapy for painful diabetic neuropathy in the United Kingdom and to determine if a larger randomized controlled trial testing treatment efficacy is justified. **Methods.** Participants with painful diabetic neuropathy were recruited online and from hospital services. This was a single-arm study in which all participants received online Acceptance and Commitment Therapy. Participants completed questionnaires at baseline and three months post-treatment. Primary feasibility outcomes were recruitment, retention, and treatment completion rates. Secondary outcomes were pre- to post-treatment effects on pain outcomes and psychological flexibility. **Results.** Of 225 potentially eligible participants, 30 took part in this study. Regarding primary feasibility outcomes, the treatment completion and follow-up questionnaire completion rates were 40% and 100%, respectively. Generally, at baseline those who completed the treatment, compared with those who did not, had better daily functioning and higher psychological flexibility. With respect to secondary outcomes, results from the completers group showed clinically meaningful effects at post-treatment for 100% of participants for pain intensity and pain distress, 66.7% for depressive symptoms, 58.3% for functional impairment, 41.7% for cognitive fusion, 66.7% for committed action, 58.3% for self-as-context, and 41.7% for pain acceptance. **Conclusions.** This preliminary trial suggests feasibility of recruitment and follow-up questionnaire completion rates, supporting planning for a larger randomized controlled trial. However, treatment completion rates did not achieve the prespecified feasibility target. Changes to the treatment content and delivery may enhance the feasibility of online Acceptance and Commitment Therapy for people with painful diabetic neuropathy on a larger scale.

Key Words: Painful Diabetic Neuropathy; Acceptance and Commitment Therapy; Feasibility Trial

Introduction

Painful diabetic neuropathy (PDN) is a complex pain condition associated with diabetes. It affects ~25–30% of people with diabetes [1,2]. The main symptoms are tingling and burning sensations in the hands and feet that can have a significant impact on daily functioning [2,3]. Psychosocial factors, such as depression, anxiety, and sleep are significantly associated with PDN [3]. At the same time, current treatment options are mainly

pharmacological and appear to produce limited benefits [4]. The experience of pain, and how pain is viewed by others, may differ in this population compared with other populations suffering from chronic pain of mainly musculoskeletal origin [3,5].

Acceptance and Commitment Therapy (ACT) is a newer contextual form of Cognitive Behavioral Therapy (CBT) that incorporates acceptance, mindfulness, and values-based behavior change [6]. It specifically focuses on increasing psychological flexibility (PF) [7], which includes six processes: acceptance, cognitive defusion, awareness of the present moment, self-as-context, committed action, and values-based actions [8].

Systematic reviews show that CBT is effective for chronic pain in general [9]. ACT has a growing evidence base for the treatment of chronic pain and appears to produce outcomes similar to traditional CBT [10,11]. ACT appears to produce better results post-treatment regarding pain-related disability in comparison to alternative treatments, such as relaxation [12].

ACT has not previously been evaluated in PDN [13]. It is designed to be broadly applicable to different types of psychological and physical problems and may be particularly suited to multiproblem cases. Therefore, ACT may be a good fit to address the multiple impacts of pain and the range of physical and psychosocial comorbidities that people with PDN can experience [13,14]. Additionally, ACT assumes that targeting a core set of behavioral processes (i.e., PF) can lead to improved functioning and quality of life generally across these different problem areas. Thus, ACT for chronic pain may also help people with PDN without requiring specific adaptations.

A current challenge is that access to CBT and ACT for pain management is limited outside of specialist centers [15]. However, online treatments may address this, and they may be cost-effective, time-efficient, more acceptable, and less stigmatizing than face-to-face treatments [16,17]. Several studies have investigated online CBT and ACT for chronic pain, all yielding moderate to large improvements in pain and disability compared with wait-list controls or other psychological treatments [15–20].

No studies have examined online ACT for PDN, despite the clear need, potential to enhance access, and potential for cost-effectiveness. Therefore, the current study aimed to test the feasibility of online ACT for people with PDN within the context of a single-arm trial to identify if a larger randomized controlled trial (RCT) would be possible and justified. The feasibility questions were whether online ACT would be acceptable to the PDN population, as reflected by adequate recruitment, follow-up questionnaire completion, and treatment completion rates. For each of these questions, a priori criteria were set against which to determine feasibility. In terms of secondary feasibility questions, effect sizes were calculated to determine whether participants who received ACT treatment would improve on pain outcomes and PF.

Methods

Trial Design

This study was an online single-arm (nonrandomized) feasibility trial. The treatment being tested was originally designed for individuals with chronic pain in general. NHS ethical approval was obtained from the Surrey Research Ethics Committee (29/1/2018, Ref: 17/LO/2047). All participants gave informed consent, and the protocol was registered at clinicaltrials.gov (NCT03700528). The study followed the ethical standards of the Declaration of Helsinki (1964) and its later amendments.

Participants completed assessment at baseline and three-month follow-up through a secure survey platform (Bristol Online Survey [BOS]). Even though the literature recommends RCT designs [17], the National Institute for Health Research [21] highlights that not all feasibility trials should be randomized. Our focus was on recruitment, retention for follow-up questionnaires, and treatment completion rates, which are aims that do not necessarily require randomization.

The total sample size was calculated to allow reliable estimation of retention and completion rates, assuming a retention rate of 80%. The estimated sample size would allow for estimation of the true population consent rate with an 11% margin of error (95% confidence interval) for eligible participants. Past research in chronic pain conducted by the team suggests consent rates between 50% and 70%, assuming a more conservative uptake of 40%, and that ~30% will meet the eligibility criteria. Additionally, a sample of 30 participants is in line with recommendations for feasibility trials [22].

Recruitment and Participants

The case definition was adults with PDN. The main inclusion criteria were 1) ≥18 years old; 2) diabetes and PDN diagnoses, which were identified through self-report questions, the Douleur Neuropathique 4 interview (DN4i), and a physician's diagnosis, when available; 3) verbal and written proficiency in English; and 4) computer literacy. Potential participants were excluded if their primary pain was not PDN. Please see Figure 1 for recruitment details. Participants were recruited via Guy's and St Thomas NHS Foundation Trust and online advertisements. Online invitations were sent and resulted in recruitment as follows: "Diabetes UK" (https://www.diabetes.org.uk/research/take-part-in-research; N = 15), "Pain Support" forum (https://painsupport.co.uk/; N = 8), "Pain Concern" forum (http://painconcern.org.uk/how-we-help/forum/; N = 4), and Twitter (N = 1). Final post-treatment questionnaires were collected in April 2019.

ACT Online Treatment

The purpose of this online therapist-supported treatment was to increase participants' PF—namely, their

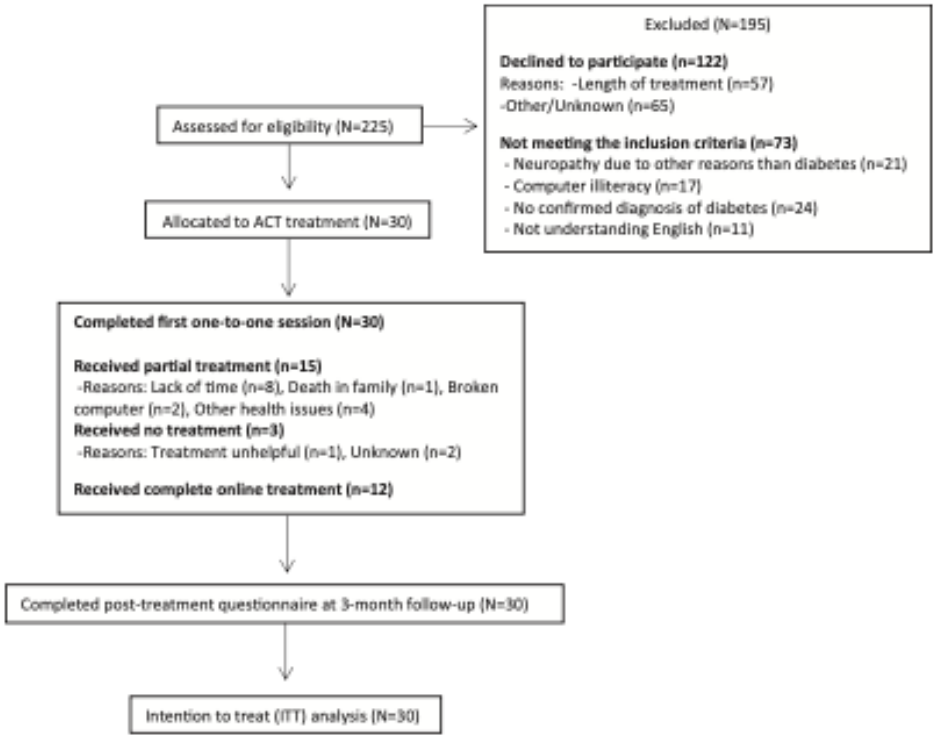

Figure 1. Study flow diagram.

willingness to experience pain, awareness of experiences in the present moment, and engagement in committed and values-based actions [10]. ACT was considered appropriate for this study, as PF is a transdiagnostic model and can be applied to various conditions with no need for any alterations [23]. ACT is theoretically well suited to a range of problem areas, and on average people with a range of conditions benefit.

Online treatment procedures and content were based on the online version of ACT, developed and initially tested by Scott et al. (2018) [15]. The online treatment platform that was used was called ACT4PAIN, initially created by LM and WS. The treatment involved one 30–45-minute Skype session with the therapist at the beginning of treatment to explain the treatment processes and set therapeutic goals. In the current study, the first author (KK) acted as the therapist. The therapist's experience level was Master's-level in health psychology, six months of certified training on third-wave CBT from the British Psychological Society (BPS), National Health Service (NHS) training on Good Clinical Practice (GCP), and further training from LMM and WS, who are registered clinical psychologists with experience providing ACT for chronic pain. WS provided ongoing supervision to discuss participants' engagement and challenging responses as they arose. As KK acted as the therapist and analyzed the collected data, direct data entry from each participant and remote/online assessment were used to reduce the influence of the researcher on the assessment.

Following the first Skype session, eight online sessions were provided in a five-week period. This standardized package was delivered, two times per week for the first three weeks and one time per week for the final two weeks. The delivery was conducted according to the originally developed treatment by Scott et al. Twice-weekly sessions were chosen earlier in the treatment to keep participants focused on the treatment and practicing new skills. This was based loosely on a previously designed treatment [24]. Frequency of treatment sessions tapered off in the final two weeks to foster greater independence in preparation for self-management after treatment completion. The sessions consisted of video- and audio-recordings that guided participants through experiential exercises, mindfulness practice, metaphors, values clarification, and values-based goal setting. Online sessions included video and audio content that was between 12 and 35 minutes in duration (see Tables 1 and 2 for more details on treatment content). The total approximate time for the content delivered from the system was ~150 minutes.

At the start of each session, participants provided ratings of their developing skills in the categories of

Table 1. Summary of Acceptance and Commitment Therapy psychological treatment sessions

Sessions	Information	Tasks/Exercises	Total Video Running Time	Total Audio Running Time
Session 1: Skype one-to-one	Introducing the treatment	Goal setting & Identify barriers	–	–
Session 2: Online	Living with pain: Shifting your focus	Passengers on the bus metaphor & Notice 5 things exercise	6.16 min	10.86 min
Session 3: Online	Open: Letting go of the struggle with pain	Unwanted party guest & Connect, breathe, open up exercise	3.99 min	12.16 min
Session 4: Online	Open: Responding differently to thoughts	Mind experiments & Labeling thoughts exercise	7.01 min	17.63 min
Session 5: Online	Engaged: Choosing your values and goals	Choosing your focus & 80th birthday exercises & Values assessment form	6.32 min	10.52 min
Session 6: Online	Aware: Focusing on the present moment	Tracking thoughts in time	7.23 min	27.08 min
Session 7: Online	Engaged: Committing to your goals	The swamp metaphor, Small steps exercises, & Goal-setting form	3.84 min	8.06 min
Session 8: Online	Aware: A different point of view	"Observer self" exercise	4.94 min	17.32 min
Session 9: Online	Building wider patterns of success	"Brief observer self-exercise," Your kind friend exercise, & Goal-setting form	4.16 min	10.87 min
Session 10: Skype one-to-one	Committed action & Debriefing	Goal setting & Evaluation	–	–

This format is based on the treatment in Scott et al.'s trial [15].

openness, awareness, and engagement, on a scale from 0 (never) to 6 (always) in reference to the past three days. These ratings were seen by the therapist, who could then use the information to tailor feedback. During each session, participants were asked about their experience with the material and received individual written feedback from the therapist within 24 hours through secure in-site messaging. The feedback was meant to be individualized, to incorporate any particular challenges specific to PDN, to encourage engagement, and to enhance PF. Participants received weekly reminders to complete sessions through messages generated by the website. When a participant expressed that they wished to drop out, the therapist would ask the reason for discontinuation, via in-site messaging, and whether the participant had any suggested refinements for the treatment that would encourage them to complete all the sessions. When sessions were completed, the therapist could see this; however, data on how frequently/for how long participants practiced the exercises between sessions were not collected. Collecting practice time information would be useful in a larger trial. However, therapist messages served to prompt practice and discuss any barriers or challenges around practicing skills between sessions. At the end of the online sessions, there was a final Skype session with the therapist to encourage participants to set long-term goals, discuss treatment, and make suggestions for improvements. Thus, there was a total of 10 treatment sessions (two Skype and eight online sessions).

Assessment Procedures

During baseline assessment, participants responded to self-report questions about diabetes and neuropathy duration, medication, comorbidities, age, gender, education, occupation, domestic status, and ethnicity. The participant self-report on the DN4i was used as a screen to support the potential diagnosis of PDN. The DN4i is a psychometrically validated tool used to screen for the possible presence of neuropathic pain. It includes seven interview questions, and a positive screen is indicated by the score of ≥ 3. The questions include a) pain characteristics (e.g., burning, electric shocks) and b) associated symptoms (e.g., tingling, numbness) [25]. This measure demonstrated good internal consistency in the current sample (Cronbach's $\alpha = 0.72$). For participants recruited from the NHS, there was also physician diagnosis of diabetes and PDN.

Primary Feasibility Outcomes

The primary feasibility outcomes for this study included recruitment, retention, treatment completion rates, and data completeness. Feasibility thresholds for these were defined a priori. The targeted sample to recruit was 30 participants. The aim was to achieve a treatment completion rate of 70% and a follow-up questionnaire completion rate of 80% [15]. Online treatment completion was calculated as the proportion of participants who completed the treatment, defined beforehand, based on Scott's et al. feasibility trial, as participants completing at least seven out of 10 sessions [15]. Thus, recruitment of 30 participants and achieving 80% follow-up questionnaire completion and 70% treatment completion would support the feasibility of a fully powered RCT.

Secondary Outcomes

Secondary to the primary feasibility aims outlined above, this study aimed to produce estimates of the magnitude of treatment effect on standard pain outcomes and PF treatment processes as preliminary assessment of potential efficacy. All clinical outcomes were assessed with psychometrically validated and reliable instruments.

Table 2. Overview of treatment's schedule

Week (0)	Week (1)	Week (2)	Week (3)	Week (4)	Week (5)	Week (6)	Week (7)	Week (12)
Participants give informed consent and respond to the baseline questionnaire	Skype session with the therapist, to help the navigation within the platform, set goals, identify barriers, and answer any questions	Completion of sessions 2 and 3	Completion of sessions 4 and 5, based upon completion of the previous ones	Completion of sessions 6 and 7, based upon completion of the previous ones	Completion of session 8, based upon completion of the previous ones	Completion of session 9, based upon completion of the previous ones	Skype session to set future goals and evaluate the treatment	Participants receive an e-mail linked to a post-treatment questionnaire
Arrange the first Skype session	Participants gain access to the online program (username, password, hyperlink)	Participants access the next sessions if they completed the previous ones	Direct messaging with the therapist	Direct messaging with the therapist	Direct messaging with the therapist	Direct messaging with the therapist	Participants receive an e-mail linked to a post-treatment questionnaire	–
–	–	Direct messaging with the therapist	–	–	–	Arrange the final Skype session	–	–

Rows follow the order of actions undertaken per week.

Standard Pain Outcomes

Pain Intensity and Pain Distress: Pain Scale. Participants rated their average overall pain intensity and distress now and during the past week on a 0 (no pain/distress) to 10 (worst possible pain/distress) numerical scale [26]. This measure has been validated in people with general chronic pain [27].

Depression Symptoms: Patient Health Questionnaire (PHQ-9). The PHQ-9 is a widely used measure of depression symptoms. It is a nine-item questionnaire rated on a 0–3 numerical scale, with the last item rated from "not difficult at all" to "extremely difficult." A higher score for the sum of the nine items indicates higher levels of depression severity [28]. This measure demonstrated good internal consistency (Cronbach's $\alpha = 0.88$) in the current sample.

Functional Impairment: Work and Social Adjustment Scale (WSAS). The WSAS is a five-item questionnaire assessing functional impairment related to one's health condition. It has been previously used in chronic pain trials [15] and focuses on domains of functioning such as work and hobbies that might be targeted within the treatment. Each item is rated on a 0 (no impairment) to 8 (very severe impairment) scale [29]. This measure demonstrated good internal consistency (Cronbach's $\alpha = 0.94$).

Patients' Global Impression of Change (PGIC). The PGIC is a single-item scale assessing participants overall perception of change after treatment [30]. On this scale, participants report their change as very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. It is routinely used in trials for chronic pain [31].

Theoretically Relevant Treatment Process Variables

Chronic Pain Acceptance: Chronic Pain Acceptance Questionnaire (CPAQ-8). The CPAQ-8 is a reliable measure of chronic pain acceptance, with each item scored on a seven-point scale. The measure reflects pain willingness and activity engagement in the context of pain [32,33]. This measure demonstrated good internal consistency in the current sample (Cronbach's $\alpha = 0.81$).

Cognitive Fusion: Cognitive Fusion Questionnaire (CFQ-7). The CFQ-7 is a measure of cognitive fusion or defusion, with items rated on a seven-point scale [34]. Cognitive defusion is the capacity to experience thoughts as just thoughts and not as events as they are directly experienced. This measure demonstrated good internal consistency (Cronbach's $\alpha = 0.97$).

Committed Action: Committed Action Questionnaire (CAQ-8). The CAQ-8 is a measure of committed action as defined in the PF model [35]. Its items are rated on a 0 (never true) to 6 (always true) scale, and they reflect the level of flexible commitment in the pursuit of meaningful goals and plans. This measure demonstrated good internal consistency (Cronbach's $\alpha = 0.86$).

Self-as-Context: Self-Experiences Questionnaire (SEQ). The SEQ, assesses self-related processes in the PF model, mostly including the capacity to see oneself as distinct from one's thoughts and feelings. The SEQ is a 15-item questionnaire in which items are rated on a 0 (never true) to 6 (always true) numerical scale [36]. This measure demonstrated good internal consistency (Cronbach's $\alpha = 0.95$).

Statistical Analyses

Data were analyzed with the Statistical Package for Social Science for Windows (version 18.0 IBM; SPSS, Chicago, IL USA). Descriptive statistics, including means and SDs for continuous variables and frequencies and percentages for categorical variables, were calculated for participant characteristics and primary feasibility outcomes.

For the clinical outcome and process variables, including pain distress and pain intensity (pain scale), depression symptoms (PHQ-9), functional impairment (WSAS), chronic pain acceptance (CPAQ-8), cognitive fusion (CFQ-7), committed action (CAQ-8), and self-as-context (SEQ), *t* tests were conducted to determine whether there were differences on the baseline scores for these variables between completers and noncompleters of the treatment. The secondary aim of the study was addressed via effect size calculations and paired *t* test analyses to examine the magnitude of the effect over time on these measures within the single group receiving treatment. In exploratory analyses, mixed between-groups and repeated-measures analysis of variance were used to examine whether treatment completion status was associated with any effects on the measures. The final set of frequency analyses addressed descriptively the participant's perception of treatment change (PGIC).

Clinically meaningful changes were also calculated following the IMMPACT recommendations, which include the convention of applying a threshold of one-half SD [37]. The value for one-half SD was calculated for each outcome for the whole sample at baseline (pretreatment). A clinically significant effect was identified where the change observed for a participant, in a specific outcome, exceeded one-half SD between pre- and post-treatment.

Results

Sample Characteristics

The mean age of participants (SD) was 51.23 (13.30) years. Men represented 56.7% of the sample, and the sample was predominantly white (67%). Equal proportions of the sample either had full-time employment (30%) or were unemployed due to pain (30%), while about a quarter were retired (23.3%). The median DN4i score of all participants was 4.00, and all participants scored higher than the cutoff (an overall score of at least 3) for neuropathic pain. The mean duration of PDN (SD) was 6.97 (1.04) years. Please see Tables 3 and 4 for detailed demographic and clinical characteristics.

Table 3. Sample demographic characteristics (N = 30)

	N (%) or M ± SD or Median (Range)
Age, y	51.23 ± 13.30
Age range 21–50 y	15 (50)
Age range 51–80 y	15 (50)
Education, y	15.20 ± 4.92
Gender	
Male	17 (56.7)
Female	13 (43.3)
Ethnicity	
White	26 (86.6)
Asian	2 (6.7)
Mixed	2 (6.7)
Living status	
Alone	5 (16.7)
With partner	10 (33.3)
With child/children	2 (6.7)
With partner and child/children	8 (26.7)
With other relatives	3 (10)
With friends/flatmates	2 (6.6)
Employment status	
Employed full-time	9 (30)
Employed part-time	3 (10)
Unemployed—due to pain	9 (30)
Unemployed—unrelated to pain	1 (3.3)
Student/training—full-time	1 (3.3)
Retired	7 (23.3)
Diagnosis of type 1 diabetes	12 (40)
Diagnosis of type 2 diabetes	18 (60)
DN4i	3.5 (0.00–7.00)
≥4	30 (100)

Range reveals the lowest and highest values, respectively.
DN4i = Douleur Neuropathique 4 interview.

Table 4. Diabetes and pain characteristics (N = 30)

	N (%) or M ± SD
Diabetes diagnosis, y	15.50 ± 2.39
Painful diabetic neuropathy duration, y	6.97 ± 1.04
Analgesic medication	
Nonsteroidal anti-inflammatory drugs	4 (13.3)
Anticonvulsants	3 (10.0)
Antidepressants	14 (46.7)
Anti-epileptics	7 (23.3)
Opioids	8 (26.7)
Other	6 (20.0)
No analgesic drugs	5 (16.7)
Comorbidities	
Retinopathy/vision impairment	11 (36.7)
Cardiac infarction	2 (6.7)
Angina pectoris	1 (3.3)
Coronary stent	2 (6.7)
Coronary bypass	2 (6.7)
Diabetic nephropathy	13 (43.3)
Dialysis	1 (3.3)
Leg/foot ulcer	3 (10.0)
Operation on legs	3 (10.0)
Amputation	1 (3.3)
Sleeping disorders	13 (43.3)
Micturition and defecation disorder	2 (6.7)
No comorbidity	7 (23.3)

Note: N is the number of participants, % is the percentage the number of participants represents in the sample, M is the mean and SD is the standard deviation.

Table 5. Baseline scores on study variables for treatment completers and noncompleters

	Completer	N	Mean	SD	*t*	*D*	*P* Value
Pain intensity (rating scales)	Yes	12	6.50	1.58	0.497	0.19	0.623
	No	18	6.13	2.15			
Pain distress (rating scales)	Yes	12	6.16	2.50	−0.334	−0.13	0.741
	No	18	6.47	2.43			
Depression symptoms (PHQ-9)	Yes	12	11.16	7.28	−2.341	−0.87	0.027
	No	18	17.00	6.27			
Functional impairment (WSAS)	Yes	12	15.92	12.29	−2.033	−0.76	0.052
	No	18	25.44	12.76			
Cognitive fusion (CFQ-7)	Yes	12	11.83	9.31	−2.133	−0.80	0.042
	No	18	21.17	13.08			
Committed action (CAQ-8)	Yes	12	33.17	8.48	2.368	0.88	0.025
	No	18	25.17	9.42			
Self-as-context (SEQ)	Yes	12	64.33	16.77	1.942	0.72	0.062
	No	18	52.28	16.58			
Chronic pain acceptance (CPAQ-8)	Yes	12	26.08	5.40	2.973	1.11	0.006
	No	18	19.61	6.11			

On pain intensity, pain distress, and depression symptom variables, a higher score means worse well-being/functioning, whereas higher scores on process variables (except cognitive fusion measure) indicate higher psychological flexibility.

CAQ-8 = Committed Action Questionnaire; CFQ-7 = Cognitive Fusion Questionnaire; CPAQ-8 = Chronic Pain Acceptance Questionnaire; PHQ-9 = Patient Health Questionnaire; SEQ = Self-Experiences Questionnaire; WSAS = Work and Social Adjustment Scale.

Primary Feasibility Outcomes

In total, 225 people were referred or expressed initial interest in the study, and 30 of these consented to participate (24.6% recruitment) during a three-month recruitment period. One hundred twenty-two (54%) declined to participate, and 73 (32%) were not eligible. Participants were recruited from Guy's and St Thomas NHS Foundation Trust (N = 2) and online advertisements (N = 28) between October 2018 and December 2018. Twelve (40%) participants completed the online treatment sessions as per the specified completion definition. All participants were retained in the trial (100%), in the sense that they completed all measures, and data completeness was 100%. Reasons for discontinuing treatment can be found in Figure 1. For the 18 people who did not complete treatment, the most frequent reasons were no time (44.4%, N = 8), other health problems (22.2%, N = 4), computer problems (10.5%, N = 2), or other (22.9%, N = 4).

Analyses of pretreatment data for pain intensity and pain distress variables revealed no significant differences between treatment completers and noncompleters. However, comparison of pretreatment scores for depression symptoms, functional impairment, chronic pain acceptance, cognitive fusion, committed action, and self-as-context variables showed large differences between completers and noncompleters. It is notable that, at pretreatment, treatment completers demonstrated lower cognitive fusion and functional impairment and higher levels of committed action, self-as-context, and acceptance than noncompleters. Please see Table 5 for more details.

Secondary Feasibility Outcomes: Clinical Outcomes

At post-treatment, all 18 treatment noncompleters (60% of the overall sample) reported "no change" in their health and functioning compared with before treatment. Among treatment completers (N = 12), all reported that they felt "improved" (N = 10) or "very much improved" (N = 2).

Each of the variables from the clinical outcome and process measures was examined for normality using histograms, Q-Q plots, skewness, and kurtosis. None of these showed significantly skewed distributions or outliers expected to adversely affect the analyses. See Table 5 for group means and standard deviations on study variables.

Effect size calculations and paired *t* test analyses of pre- and post-treatment scores for the full sample revealed small effects over time for depression symptoms and functional impairment and medium effects for pain intensity and pain distress, chronic pain acceptance, cognitive fusion, committed action, and self-as-context. These results included a mix of improvements in some variables and deterioration in others, owing particularly to deterioration in the larger treatment noncompleters (Table 6). However, the majority of the sample did not complete treatment, and therefore, an improvement in the full sample analysis was not necessarily expected. The analysis of time by completer, which was conducted, showed that some of these variables improved among the completers.

Exploratory Analyses of Treatment Completion and Clinical Outcomes

Large interaction effects between time point and treatment completion were observed across all variables examined, except for chronic pain acceptance, where the effect was very small. The large effects included pain intensity, pain distress, depression symptoms, functional impairment, cognitive fusion, committed action, and self-as-context. Please see Table 6 for more details.

Table 6. Paired *t* test uncontrolled analysis and repeated-measures ANOVA examining psychological flexibility variables in completers (N = 12) and noncompleters (N = 18)

Paired T Test Uncontrolled Analysis

	Pretreatment Scores		Post-treatment Scores				
	Mean	SD	Mean	SD	*t*	*D*	*P* Value
Pain intensity	6.28	1.92	5.05	3.64	1.59	0.42	0.124
Pain distress	6.35	2.42	5.28	3.88	1.29	0.32	0.208
Depression symptoms	14.67	7.187	14.27	9.00	0.26	0.05	0.795
Functional impairment	21.64	13.24	22.67	15.91	−0.34	−0.07	0.736
Cognitive fusion	17.43	12.44	24.87	15.15	−2.58	−0.53	0.015
Committed action	28.37	9.76	22.50	15.71	2.23	0.44	0.034
Self-as-context	57.10	17.43	39.53	29.37	3.41	0.72	0.002
Chronic pain acceptance	22.20	6.58	24.00	4.15	−1.74	−0.32	0.092

Time*completer interaction effects

		Pretreatment Scores		Post-treatment Scores					
	Completer	Mean	SD	Mean	SD	MS	*F*	d_{ppc2}*	*P* Value
Pain intensity	Yes	6.50	1.58	0.83	0.72	196.54	82.89	3.76	0.000
	No	6.13	2.15	7.86	1.17				
Pain distress	Yes	6.16	2.50	0.75	0.45	189.23	48.29	2.93	0.000
	No	6.47	2.43	8.31	1.19				
Depression symptoms	Yes	11.16	7.28	4.08	3.23	446.67	21.94	−1.65	0.000
	No	17.00	6.27	21.06	3.06				
Functional impairment	Yes	15.92	12.29	3.92	3.32	1,698.68	20.55	−1.71	0.000
	No	25.44	12.76	35.17	3.33				
Cognitive fusion	Yes	11.83	9.31	7.17	2.62	1,464.10	19.19	−1.08	0.000
	No	21.17	13.08	36.67	4.33				
Committed action	Yes	33.17	8.48	40.25	5.15	1,677.03	35.26	2.36	0.000
	No	25.17	9.42	10.67	5.78				
Self-as-context	Yes	64.33	16.77	73.42	7.90	7,102.23	44.44	2.64	0.000
	No	52.28	16.58	16.94	8.98				
Chronic pain acceptance	Yes	26.08	5.40	28.33	2.27	2.03	0.12	−0.13	0.729
	No	19.61	6.11	21.11	2.00				

ANOVA = analysis of variance.
*d_{ppc2} (pretest–post-test–control): according to Morris [38].

This was confirmed when data were split into completers and noncompleters of the treatment. For completers, there were significant improvements within-group over time, including a large effect for pain intensity and pain distress, depression symptoms, and functional impairment. These results appear superior to those of participants who did not complete the treatment, who generally deteriorated.

Over time, completers improved and demonstrated a large effect for committed action compared with noncompleters, who had lower scores and a similarly large effect in the opposite direction. Completers showed a medium effect for cognitive fusion and self-as-context. On the other hand, noncompleters over time reported significantly higher levels of cognitive fusion and lower levels of self-as-context. There were medium effects for completers and noncompleters for chronic pain acceptance.

Clinically Meaningful Changes

The percentage of completers and noncompleters who experienced clinically meaningful changes can be found in Table 7. At post-treatment, the majority of treatment completers showed meaningful improvements for seven out of eight of the outcome variables. The exception was chronic pain acceptance, where 41.7% meaningfully improved, while 50% did not meaningfully change. Very few of the completers deteriorated meaningfully. For four of the outcomes, there were none, and for the others, there was one participant. For the noncompleters, the picture of meaningful change was more mixed. In six of eight outcomes, 72% or more of the participants either showed no meaningful change or meaningfully deteriorated. For just two outcomes, the majority meaningfully improved (for committed action and self-as-context, which was unexpected). For pain intensity, pain distress, and depression, the majority of noncompleters deteriorated.

Conclusions

The aim of this study was to assess the feasibility of conducting a larger RCT of online ACT for people with PDN. The targeted sample size was recruited (N = 30), and all participants were retained in the trial and

Table 7. Percentages of completers and noncompleters who made clinically meaningful improvements, showed no change, and deteriorated post-treatment

	Completers (N = 12)			Noncompleters (N = 18)		
	Improved (%)	No Change (%)	Deteriorated (%)	Improved (%)	No Change (%)	Deteriorated (%)
Pain intensity	12 (100.0)	0 (0.0)	0 (0.0)	2 (11.1)	4 (22.2)	12 (66.7)
Pain distress	12 (100.0)	0 (0.0)	0 (0.0)	3 (16.7)	4 (22.2)	11 (61.1)
Depressive symptoms	8 (66.7)	4 (33.3)	0 (0.0)	2 (11.1)	6 (33.3)	10 (55.6)
Functional impairment	7 (58.3)	5 (41.7)	0 (0.0)	1 (5.6)	10 (55.6)	7 (38.9)
Cognitive fusion	5 (41.7)	6 (50.0)	1 (8.3)	1 (5.6)	4 (22.2)	13 (72.2)
Committed action	8 (66.7)	3 (25.0)	1 (8.3)	16 (88.9)	0 (0.0)	2 (11.1)
Self-as-context	7 (58.3)	4 (33.3)	1 (8.3)	18 (100.0)	0 (0.0)	0 (0.0)
Chronic pain acceptance	5 (41.7)	6 (50.0)	1 (8.3)	5 (27.8)	7 (38.9)	6 (33.3)

Percentages are rounded up to 1 decimal digit.

completed follow-up questionnaires. However, the treatment completion rate was 40%, which was below the prespecified feasibility target of 70%. Hence, partial feasibility was found for the research and treatment methods for evaluating online ACT for PDN in a larger RCT. The treatment completion rate here is considered inadequate to justify proceeding to a full-scale trial until some modifications to enhance treatment engagement are designed and demonstrated.

The treatment completion rate for the current treatment was 40%, which is lower than a Dutch trial (72%) [19], a German trial (60%) [39], and a UK trial (61%) [15] of online ACT for general chronic pain. In the current study, there were differences at baseline between treatment completers and noncompleters, even though the sample was largely self-selected online, and these differences may underlie the high dropout rate. Particularly, noncompleters had relatively higher levels of cognitive fusion, depressive symptoms, functional impairment, and lower levels of committed action, pain acceptance, and self-as-context. This appears not to have been found in other similar studies [15,19,39] and may be unique to the PDN population, perhaps due to the complexity or nature of neuropathic pain, or it could be due to some unique aspect of the setting or methods used here. As this is a one-time finding in a small sample, it is too soon to determine what it means.

If further research again shows that factors such as higher levels of cognitive fusion, depressive symptoms, and functional impairment and lower levels of committed action, pain acceptance, and self-as-context are associated with inadequate treatment completion, then it could be used either in selectively allocating participants to treatment, as targets for pretreatment intervention, or as a basis for redesign of the treatment methods or content. Presumably, selecting participants with relatively lower depression or functioning impairment as a group may result in better completion rates.

It may be that participants with particularly low levels of PF or severe depression and high pain interference require more intensive psychological therapy, such as that delivered in a face-to-face setting (individual or group). However, it is known from previous studies that online treatment completion rates can be low, apparently due to problems with the use of technology, barriers due to poor health, or low motivation [40]. Based on our data, it is not known whether it was the ACT approach itself, aspects of online delivery, requirements inherent in any psychological treatment, or all of the above that was unacceptable to participants. Most of those who did not complete treatment reported a lack of time. Another possible explanation represented in supplemental background information was that 11/30 reported some degree of visual impairment, which would make it difficult for them to complete treatment that mainly consisted of videos. Each of these possibilities deserves further consideration.

Future research may explore treatment engagement through a qualitative study to investigate PDN participants' preferences for delivery format and views about ACT as a treatment approach. The model underlying ACT suggests that a core set of behavioral processes underlie the treatment impact and that a standard package of this treatment ought to be generally applicable. However, our data suggest that the treatment may need to be better tailored in a PDN context. This could be achieved by providing specific case examples of PDN throughout and orienting participants to problem areas specific to PDN such as fear of falling [2,3]. Treatment might also focus more explicitly on improving sleep. Given that 13/30 of the participants reported significant sleeping problems, this could be a motivating element if added to the treatment. A qualitative study could help to further identify specific problem areas within PDN for which to apply ACT skills. This could contribute to better tailoring the treatment for this population and enhance engagement.

Another way to potentially enhance treatment engagement is to allow the treatment to be more dynamically customizable around each individual. This could include remotely assessing each case intensively over time, supporting the selection of treatment modules that are personalized, and delivering only the modules particular participants need and not the ones they do not, leading to

more rapid and efficient benefits from treatment [41]. In theory, a customized modular treatment guided by daily data gathering could pick up on, and intervene in, engagement lapses to promote better completion rates. The treatment components delivered here could certainly be repackaged to operate in this fashion.

The observed uncontrolled effect sizes on the clinical outcomes and process measures ranged from small to large at three months, favoring a decrease of depression symptoms, functional impairment, pain intensity, and pain distress and an increase of chronic pain acceptance and committed action in treatment completers. Although clinical outcome results are highly preliminary, the large reduction in pain differs from other ACT trial results. This may be relevant to the observation in a recent cross-sectional survey that PF may play a smaller role, compared with pain intensity, in relation to distress and disability in the PDN population [13].

The rate of clinically meaningful results for treatment completers across outcomes are encouraging. At post-treatment, all treatment completers showed meaningful improvement in at least three variables, 83.3% in at least four variables, 41.7% in at least five, 33.3% in at least six, 25% in at least seven, and 16.7% in eight. On the other hand, all noncompleters showed a meaningful deterioration in at least two variables, and half of noncompleters deteriorated in at least half (four of eight) of the outcomes. These results may provide "proof of concept" that ACT can benefit people suffering from the effects of PDN, provided that they can be supported to complete the treatment sessions. On the other hand, support for applying ACT in this context may only apply to people who are relatively higher in functioning and PF.

A notable result is the number of clinical outcome and process measures on which those who did not complete treatment worsened during the three-month interval examined. In fact, on every measure, with the exception of pain acceptance, the noncompleters were worse at the end of the trial compared with the beginning. In several cases, these declines were significant and large, and in all cases this was unexpected. This perhaps reflects natural variability in PDN, and perhaps this contributed in some way to noncompletion, but this is only speculation [40,42]. Another possible explanation might be that the treatment did not adequately target key areas of need for participants. For example, depression is highly prevalent in people with diabetes and in those with diabetes complications. Therefore, not only does this population have significant levels of pain, but they also have comorbid disability because of PDN, like balance and mobility problems, and associated microvascular comorbidities, such as retinopathy and nephropathy [43]. These comorbidities were not adequately measured or reported for this sample. Qualitative interviews with the noncompleters would have allowed us to determine the reason for these changes and the main reason for discontinuing treatment. Also, a revised version of treatment might help participants to practice applying these skills more broadly to other diabetes-related problems, which might be considered to have a larger impact on their functioning and quality of life.

Possibly, noncompleters were experiencing symptoms of PDN during their engagement in this treatment, became more conscious of their experienced difficulties, and were willing to report them. Additionally, it is possible that the nature of neuropathic pain is responsible for noncompletion of treatment. It may be relevant that neuropathic pain is different pathophysiologically, compared with other chronic pain conditions, with the dominant component of neuroplastic changes within the nervous system [44]. These speculations deserve study.

In this study, the most commonly suggested refinements by the noncompleters, coming from comments in the experiential exercises or the last Skype session with the therapist, were to shorten audios and videos, add more face-to-face sessions, provide more educational material on diabetes and neuropathy, and provide additional printed materials to supplement the online content. We note, however, that the total time for all online content was just 150 minutes, or an average of less than 19 minutes for each online session. Nonetheless, it could be possible to provide choices around longer exercises by more clearly alerting participants regarding the length and providing them with scheduling options (now or later when there is more time available) or by providing a choice for several shorter exercises in the place of a lengthy one. A missed opportunity here, to investigate treatment noncompletion, would have been to include in-depth exit interviews with participants who dropped out. Unfortunately, this method was not possible in the current study due to lack of resources. Such a study could provide more detailed feedback on reasons for dropping out or losing interest.

This study has several limitations. First, the study design does not allow for causal interpretations for observed changes in outcomes, as this was not an RCT. Second, even though the recruitment target was reached (N = 30), this is a small sample with high dropout rates (60%), which may lead to limited reliability and precision of our estimates and limited power for all of the mean comparisons. The sample was also too small to conduct meaningful analyses to identify characteristics associated with a favorable response to treatment responses. Third, the fact that participants were self-selected to take part in the treatment means that results may not generalize to the wider population of people with PDN in need of treatment. Also, as the majority of participants were recruited from online portals, and even though we used the DN4i and self-reported questions for diabetes and PDN diagnosis, there is the possibility that participants did not fulfil more stringent diagnostic criteria for PDN. It is worth noting that the treatment applied here was designed for people with chronic pain in general. In retrospect, this is possibly not an ideal test for the

specific feasibility for people with PDN, and a more tailored version of treatment may ultimately be more feasible. Finally, it is recognized that a different sample and longer follow-up may yield different results. The generalizability and reliability of the results still need to be established.

Despite these limitations, this is the first feasibility study of online ACT in people with PDN. Based on low completion rates, a larger RCT testing efficacy is not feasible for the current online ACT treatment as examined here. Future research is encouraged to specifically address the problem of low treatment completion, possibly including active patient involvement and qualitative work. Further tailoring of research methods and treatment to specifically fit PDN may be needed. Another avenue, at the same time, is simply greater individualization. This could include identifying the defining features of individuals who will both engage in and achieve clinically meaningful benefits from the treatment model here, and those who will not. It could also include making this treatment more sensitive to whoever encounters it by breaking it into modules and personalizing the delivery of these based on assessment data.

Authors' Contributions

KK, the first author, responsible for the work as a whole, recruited patients, delivered the treatment, collected and analyzed the data, and produced the first draft of the manuscript. LM and KW contributed to the conception, design of the study, and research plan, offered their guidance on protocol and selection of assessment tools, and edited and approved the final version of the manuscript. WS contributed by offering guidance throughout the treatment delivery and statistical analysis plan and revised, edited, and approved the manuscript. EG supported the project, offered guidance and expertise, and revised, edited, and approved the final version of the manuscript.

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